Patient knowledge of and preferences for oral anticoagulation and vitamin B_{12} in the context of medication adherence

Inauguraldissertation

zur
Erlangung der Würde eines Doktors der Philosophie
vorgelegt der
Philosophisch-Naturwissenschaftlichen Fakultät
der Universität Basel

von
Corina Kyriaki Metaxas
aus Basel (BS)

Basel, 2018

Genehmigt von der Philosophisch-Naturwissenschaftlichen Fakultät
auf Antrag von:

Prof. Dr. Kurt E. Hersberger

Prof. Dr. med. Dimitrios Tsakiris

Basel, den 12. Dezember 2017

Prof. Dr. Martin Spiess

Dekan

1 Acknowledgments

First and foremost, I would like to thank my supervisor Prof. Kurt Hersberger, who offered me a warm welcome in the PCRG family and kindly introduced me into the world of Pharmaceutical Care. Thank you for your motivation, inspiration and your constant belief in me and this challenging project. I always considered myself to be well supported (scientifically and personally) as you always had advices for every new and sometimes tricky situation I faced whilst working on my PhD. Thanks also for all the fruitful discussions we had, your constant encouragements and for sharing your immense knowledge with me. I am very grateful that you passed all of that worldly wisdom to me. The possibility to do a PhD in the inspiring working environment of the PCRG motivated me to become a better researcher and pharmacist.

I would like to express my special appreciation and thanks to my supervisors PD Dr. Isabelle Arnet and Dr. Philipp Walter. This thesis would not have been possible without their immense experience, support and knowledge.
Thank you Isabelle, for your precious and thoughtful inputs. I very much appreciated how you were able to discuss and find solutions to all my numerous questions within a short length of time. I am very grateful to Philipp for supporting me, in finding my own research projects and for his guidance through the laboratory part of my thesis. I was able to benefit a great deal from your immense knowledge and experience in clinical chemistry, whilst your constructive feedback and pragmatism was very much appreciated.

Many words of thanks to Prof. Dimitrios Tsakiris for giving me valuable advices during my thesis and for accepting the role of the co-referee in this thesis despite all of your many other obligations.

Many thanks to Prof. Henriette Meyer zu Schwabedissen for accepting the function of representative of the faculty.

I am most grateful to all collegues of the PCRG family, namely, Kurt Hersberger, Isabelle Arnet, Markus Lampert, Philipp Walter, Jean-Pierre Rothen, Vera Bernhardt, Esther Spinatsch, Verena Renggli, Sandra Unfer, Susanna Papa, Corinne Spaar, Fabienne Abt and of course “Kurt’s Gang”: Fabienne Böni, Markus Messerli, Carole Kaufmann, Karen Maes, Samuel Allemann, Dominik Stämpfli, Valerie Wentzky, Tamara Imfeld, Helene Studer, Melanie Haag, Lea Brühwiler and Claudia – it was a great pleasure to travel the PhD-journey toghether with you. I enjoyed being

part of the family. Particularly, I will always remember all the fun moments we shared i.e. when mastering the rapids of the Aare in our *Bötlis*, running our bicycles through the odysseys to *Kurts Weiher* and the *petite camarque,* the legendary ski weekends, and much more. My special thanks go to Markus for helpful advice and support in several research project. Thank you Valerie for your valuable input and help in the “anticoagulation”- studies. I thank my super-fast proofreaders Benji Berger, William Caddy, Sandra Unfer, Melanie Haag, Dominik Stämpfli and Helene Studer. Finally, and most importantly, thank you for your scientific and non-scientific support, the good moments together and the pleasant work environment!

I would also like to thank all of you who supported me and shared your experiences with me along my postgraduate education in clinical pharmacy, namely Markus Lampert, Fabienne Böni, Maya von Moos, and Seraina Mengiardi-Nemec. I am very grateful to Andrea Studer for being my supervisor for this further education, and for giving me valuable advice on clinical pharmacy in practice. Thank you that I could count on you whenever I needed advice. A heartfelt thanks to Hanh Pham, for the good time we spent preparing the ward rounds and having fun after work.

I owe special thanks to the following persons for their collaborations. A big thank you to my MSc students Chantal Zurwerra, Susanne Habegger and Sonja Luginbühl for your excellent work and valuable contributions. I appreciated very much co-operation with Dr. Cyrill Jeger who made the “preference and biomarker response”- study in vitamin B_{12} deficient patients possible. Thanks also to his team, namely Angela and Neslie, for the pleasant cooperation. Many thanks to Prof. Gottfried Rudofsky for sharing his experiences and for his support in the “vitamin B_{12} metformin” - study. Thanks to the laboratory technicians at the Institute of Laboratory Medicine and at the Aarelab in Olten for their practical contribution. I wish to thank Dr. Mathias Stahl for sharing your contacts and thereby realizing the pilot of the “KODOA validation”-study on the wards of the Kantonsspital Bruderholz. A very special thank you, to Ursula Zoli (Aarelab, Olten) who supported me with the organization of the laboratory samples. I am very thankful for your engagement throughout these last 4 years. I enjoyed very much our lunches and your friendship. Many thanks to all who contributed to the development of the KODOA-test and/or the educational manual for the DOAC validation study (Lukas Baumann, Katarina Borer, Felix Schläfli, Christina Schrattner, Stephan Ness, Dr. Claus Diermayer, PD Dr. Thomas Dieterle, PD Dr. Balthasar Hug, Dr. Markus Mutschelknauss, Prof. Dimitrios Tsakiris, Prof. Andreas Zeller, Dr. Ottenheinrich Eichhorst, Prof. Kurt Hersberger, Dr. Markus Messerli, Verena Renggli, Susi Thürkauf). A very special thank you to the Team of the Gartenstadt-Apotheke for supporting my research projects in daily practice with

their active engagement in patient recruitment and for sharing good times. Moreover, many thanks to all the general practitioners, community pharmacists and students who recruited patients for our studies and all participating patients and pharmacists!

I thank my family and friends for bringing balance in my life: Thank you Noemi, Steffi, Lina, Jasmin, Orphee, Melina, and Sabine, Jimena, Romana, and Nicole for your friendship and all the easygoing hours we had together. A special thank you to Vali, you where there – always. My deepest thanks go to my mother Jacqueline and my father Dimitrios, who taught me to never give up and for their constant support. A heartfelt thank you to my godmother Lilly for your personal support and our discussions on my PhD journey. I thank my brother Jannis, his fiancée Nadine, with Ilias and Olga, with Mark and Alexander for helping me out during this busy time. Most of all, I would like to thank my fiancé Jan Müller, for always being there by my side during my PhD. When everything seemed too complex, you were always able to encourage me with your humor and support - thank you for your belief in me and your love!

INDEX

2 Abbreviations

AF	Atrial fibrillation
A14	Adherence scale 14
BMQ	Beliefs about medicines questionnaire
DM	Diabetes mellitus
DOAC	Direct oral anticoagulants
DVT	Deep vein thrombosis
DPPR	Daily patient possession ratio
EHRA	European heart rhythm association
HCP	Health care professionals
HoloTc	Holotranscobalamine
Hcy	Homocysteine
INR	International normalized ratio
i.m.	Intramuscular
i.v.	Intravenous
iPACT	International pharmacists for anticoagulation care taskforce
KODOA	Knowledge of direct oral anticoagulants
MEMS	Medication event monitoring system
Met	Metformin
MMA	Methylmalonic acid
MMAS	Morisky medication adherence scale
MPR	Medication possession ratio
MUR	Medicines use review
NOAC	Non vitamin K oral anticoagulants
OAC	Oral anticoagulation therapy
PE	Pulmonary embolism

P-gp	P-glycoprotein
PPI	Proton pump inhibitors
POEMS	Polypharmacy electronic monitoring system
PMC	Polymedication check
s.c	Subcutaneous
SDM	Shared decision-making
SPCs	Swiss summaries of product characteristics
SF-12	Short form 12
S-THOFLA	Test of functional health literacy in adults
T2DM	Type 2 diabetes
VB12	Vitamin B12
VKA	Vitamin K antagonists
WHO	World Health Organization

3 Summary

Adherence is defined as “the extent to which a person's behavior - taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider”. Level of adherence to medication varies greatly and is related to treatment, patient and /or health care provider. The WHO stated in 2003 that adherence to long-term therapies in the general population is around 50% in developed countries. Non-adherence to medication is a complex, common healthcare problem and can be distinguished in unintentional and intentional non-adherence. It has been shown that poor medication adherence may cause toxicity or lack of efficacy, disease progression, lower quality of life, drug resistance, medication waste and hospital admission what results in costs of approximately 100 billion a year in the United States. Therefore, detection of non-adherence and interventions aiming at improving adherence are critically important. Adherence assessment methods can be broken down into direct and indirect methods. Each method has advantages and disadvantages. Within this thesis, different adherence assessment methods were applied including subjective self-reported measures (questionnaires) and objective measures such as electronic monitoring, rates of prescription refills and measurement of biomarker levels.

In general, interventions to improve adherence can be divided into behavioural, technical, educational, and multifaceted methods. Behavioural interventions usually provide feedback, reminders or rewards to patients. Reduction of regimen complexity and use of fixed-dose regimen are examples for technical interventions. Educational interventions include patient education, provided to individuals or in group sessions using verbal, audio-visual or written material. Effectiveness of multifaceted approaches using combinations of different intervention types has been demonstrated in long-term situations. However, current methods of improving medication adherence for general chronic diseases are mostly complex and evidence of their effects remains low.

Patients have to make important health decisions that affect health outcomes. Furthermore, patients can play an important role in protecting their own health and taking appropriate action in acute episodes of ill health, as well as managing chronic illness. In particular, the management of chronic diseases, such as atrial fibrillation, require a high level of self-care skills that are determined by patients’ health literacy. Overall, health literacy can be described as the people’s capacity to manage their health. Patient knowledge about medical conditions and treatment regimen is an important aspect of health literacy. Patient medication knowledge or shortly named

in this thesis “patient knowledge” refers to patient health knowledge related to medications including what is being used, why it is being used as well as instructions and precautions about certain medication. Lack of knowledge about medication and difficulties in understanding medication information may be related to misapprehension of instructions and/or symptoms, medication errors, low self-care behavior, poor health outcomes, and frequent visits to the emergency department. Therefore, detection of knowledge gaps and educational counselling about medication should be integrated in daily practice. Up to now, however, counselling practice in general practitioners’ practices and community pharmacies tend to concur on the relative poverty of such medication discussions. Therefore, it is not surprising that outpatients lack knowledge about their medication.

For some therapies such as oral anticoagulation therapy (OAC), there is still insufficient evidence to draw definitive conclusion regarding the impact of educational interventions on therapeutic outcomes in patients, mostly due to the inhomogeneity of the study designs. Thus, educational contents need to be prioritized, educational domains should be standardized and validated instruments for the assessment of deficit knowledge are needed to demonstrate the impact of educational counselling on outcomes in clinical trials. Further, detection of knowledge gaps and individualized educational counselling enable patients to develop preferences and take appropriate health decisions.

Patient preferences result from unique values (i.e. potential benefits, convenience) and concerns (i.e. potential harms, costs) that are formed by patient knowledge, experiences, and reflection. Having preference for a treatment mirrors the patients evaluation of these values and concerns in comparison with an alternative treatment option. For a given disease, different patients may have different preferences. Patients bring their preferences to a clinical encounter that should be integrated in decision making whenever they are to serve the patient. It has been shown that knowledge about patient preferences for a certain disease might lead to better-informed decisions in practice and in health policy. A better understanding of patient preferences is pivotal for shared decisions and important for increased adherence and ultimately patient health outcomes. Patient preferences in treatment-related decisions should be elicited and taken into account, because patients who felt less empowered with regard to treatment decisions reported lower rates of adherence. Assessment of patient preferences and Shared Decision Making is particularly recommended for situations with two or more equivalent available treatment options and similar treatment consequences for a patient’s daily life. The substitution of vitamin B_{12} (VB12) in deficient outpatients is one example where the evidence for equivalent efficacy between oral and

intramuscular application offers to patients both treatment opportunities with similar clinical outcome.

The goal of this thesis was to assess patient knowledge of anticoagulation and patient preferences for VB12 therapy and to develop an educational program on adherence for outpatients with rivaroxaban therapy. We approached this goal with four individual projects:

Project A:

- Investigation of patient knowledge of OAC in Swiss community pharmacies in an observational study.
- Development and validation of a self-assessment questionnaire for patient knowledge on direct oral anticoagulants (DOAC).

Project B:

- Assessment of the impact of type 2 diabetes and metformin use on VB12 associated biomarkers and their suitability to reflect VB12 supply.
- Exploration of patient preferences for and biomarker levels after oral and intramuscular vitamin B12 substitution.
- Investigation of patient preferences for oral and parenteral treatment in various diseases through literature review.

Project C:

- Translation and validation of the 8-item Morisky Medication Adherence Scale in German.
- Comparison of one subjective with one objective adherence score in a pilot study.

Project D:

- Development of a study protocol for a stepwise educational program on adherence for patients on rivaroxaban using feedback from electronic monitoring.

Overview of the projects:

Project A

Study A-1 aimed at screening for knowledge gaps about OAC in outpatients. We therefore amended the basic Polymedication Check (PMC) with specific open-ended questions on OAC and assessed its impact on knowledge in an observational study. Patients treated with vitamin K antagonists (VKA) or direct oral anticoagulants (DOACs) received an amended PMC. The study demonstrated that the majority of patients had knowledge gaps concerning OAC and that half of the patients did not know how to proceed in case of a missed dose. Identification of knowledge gaps led pharmacists to provide education spontaneously. Although verbally unstructured, the provision of this targeted and tailored education increased patient knowledge about OAC. We further found a trend that patients with DOAC therapy were more likely to have knowledge gaps compared to patients on VKAs. These observations served as a rationale for further studies on knowledge of DOAC, in particular the development and validation of a specific questionnaire to self-assess knowledge of DOAC (**Study A-2**).

In **Study A-2**, we followed an evidence-based approach to select relevant items for patient knowledge of DOAC. After literature review, completeness of retrieved items were exhaustively verified and supplemented with Swiss summaries of Product Characteristics (SPCs), the Update EHRA Practical Guide on the use of non-vitamin K antagonist anticoagulants, and the patient guide for taking DOAC from the cardiology patient page. Twelve anticoagulation experts across different professions participated in the questionnaire development process to ensure content validity and selection of relevant items. The developed Knowledge Of Direct Oral Anticoagulants (KODOA) test was validated in patients on DOAC and pharmacists. The KODOA-test confirmed to be feasible, comprehensive, reliable and valid to self-assess patient knowledge of DOAC. Construct validity was supported by significant differences in scores between patients and pharmacists. Finally, the KODOA-test was responsive to educational counselling about DOAC supporting construct validity.

Project B

Several cross sectional studies and case reports have presented an increased frequency of VB12 deficiency among patients with type 2 diabetes (T2DM). Because VB12 deficiency is a reversible cause of demyelinating nervous system disease and bone marrow failure, its early detection is important. Literature suggests that clinical biochemistry of VB12 is influenced by diabetes and its treatment. Therefore, **Study B-1** aimed to assess the impact of T2DM and metformin use on VB12

associated biomarkers and their suitability to reflect VB12 supply. Differences of VB12, holotranscobalamine (HoloTc), the biologically active fraction %AB12=HoloTc/VB12*100 and homocystein (Hcy) were analysed i) among diabetic outpatients with and without metformin use and ii) compared to an external non-diabetic reference group with low level of VB12 (<200pmol/L). We found that metformin treatment alone did not explain the altered VB12 metabolism as reflected by VB12 and HoloTc serum levels in all T2DM patients. Further analysis focused on VB12-deficient subgroups and included non-diabetic patients. In this sample, a significant difference of the %AB12 was observed and confirmed by multiple regression analysis. However, the model explained only 9.2% of the variance observed. These results suggest that VB12 metabolism is affected by diabetes itself as well as by other factors, which were not included in the model. Further, stepwise multiple regression analysis included HoloTc as independent variable to explain variance in Hcy levels and not VB12. Thus, HoloTc seems favorable compared to VB12 to predict hyperhomocysteinemia caused by VB12 deficiency in T2DM patients.

Study B-2 was a prospective randomized unblinded parallel group trial. Patients were recruited by their general practitioner and randomly assigned to oral or intramuscular (i.m.)VB12 treatment. Group O-oral received oral daily 1000µg cyanocobalamine for 28 days and group I-i.m. received 4 weekly injections of 1000µg hydroxocobalamine. Blood samples were analyzed for VB12, HoloTc, Hcy and methylmalonic acid (MMA). Before and after treatment, patients were asked to fill in a questionnaire about their preferences. After 28 days of treatment with high-dose VB12 administered either by oral or i.m. route, median levels of VB12-associated biomarkers were normalized in both groups. Contrary to prior studies, we observed an exaggerated response after i.m. administration and therefore the hypothesis for non-inferiority of oral in comparison to i.m. treatment had to be rejected. Because we used electronic punch cards and monitored an almost perfect intake of tablets (99.6% taking adherence), non-adherence was ruled out as a contributor to the less pronounced biomarker response. We found that initial rating in favor of either i.m. or oral therapy changed over time. However, the majority of patients preferred oral treatment before and after the study. The literature review (**Study B-3**) across different diseases yielded similar results: A majority of patients prefer oral treatment.

In order to investigate patient preferences for oral and parenteral treatment in various diseases, we conducted a literature research in the databases PubMed, EMBASE and Web of Science using the terms “patient preference” OR “patients’ preference” OR “patient perspective” AND “oral treatment” AND “inject*” (**Study B-3**). Our search was limited to original research articles that have been published after 1980, were accessible online and included intravenous, intramuscular or

subcutaneous parenteral therapy options. Our search strategy delivered 74 articles of which 62 were excluded. One article was included by cross-referencing. Eleven out of 13 articles reported preference for the oral administration (84.6%). Out of the 13 articles retrieved, five concerned cancer therapy, three antibiotic therapies, two vitamin deficiency and three other indications. Oral or parenteral therapy was preferred according to the disease. Associated factors for the preferred route of administration varied between the studies. Most articles reported convenience as an important factor to influence preference, either in favour of the oral or the parenteral therapy.

Project C

Study C-1 aimed to translate and validate the 8-item Morisky Medication Adherence Scale (MMAS-8) in German against objective and subjective measures of adherence in cardiovascular patients with polypharmacy. Validation took place on a convenient sample of ambulatory patients on chronic antiplatelet therapy. Objective adherence was obtained from electronically monitored multidrug punch cards. Internal consistency was assessed using Cronbach's alpha coefficient, construct validity using exploratory factor analyses and correlations between MMAS-8D and related measures. Convergent validity was assessed with a subjective questionnaire about beliefs about medicines (BMQ Specific, 2 subscales). A total of 70 patients were included in the study (mean score of MMAS-8D was 7.5 (SD 0.8; range 4.5-8)). Moderate internal consistency (alpha = 0.31) was observed, due to multidimensionality of the scale. Factor analysis yielded four components that accounted for 71.7% of the total variance. Convergent validity was supported by significant correlations with BMQ Necessity ($r= 0.31$; $p<0.01$), BMQ Concerns ($r= -0.16$, $p<0.05$) and with electronic adherence reports (U-values 44 and 471, $p<0.05$). Platelet aggregation values were within therapeutic range for 80% of the patients. Antiplatelet blood values within therapeutic range were associated with a higher MMAS-8D score (U-value 125, $p<0.05$).

Study C-2 aimed to assess whether the affirmative answer to the PMC question "Do you sometimes forget to take your medication?" coincides with a Medication possession ratio (MPR) <90% (non-adherence) in DOAC treated patients. For the pilot study, fifth-year pharmacy students recorded one PMC with an anticoagulated patient during internship in community pharmacies. Patient's refills of the past 12 months were used to calculate a MPR if at least two refills were available. A total of 25 documented cases were included for analysis, of which all concerned patients treated with rivaroxaban. Refills (mean of 2.9±0.8 per patient) were available for a mean of 128±62 days. MPR ranged from 50.2 - 182.7%. MPR below 90% was observed in 4 patients (16%), out of them two self-reported to sometimes forget to take the DOAC. Two further patients reported non-adherence but showed a MPR >90%. Oversupply up to 110% was observed for 7

patients, and excessive oversupply for 6 patients (MPR: 114-183%). Consideration of composite adherence measures to get a more detailed picture of adherence and experiences with educational counselling about OAC have further been implemented in **Project D**.

Project D

Study D aimed to develop a study proposal to demonstrate the impact of a tailored and stepwise educational program to rivaroxaban on adherence. Otherwise than in the previous project on knowledge about OAC (**Project A**), educational counselling was foreseen to be offered in a repetitive manner according to patient needs. Additionally, visualizing of intake pattern obtained with the electronic monitoring should be employed for providing feedback based on the individual patient profile and stressing the need of time adherence, or adapting the treatment plan in collaboration with the physician. This study will be executed beyond this thesis.

The following conclusions could be drawn:

Project A: Patient knowledge about oral anticoagulation therapy

- A majority of outpatients show knowledge gaps concerning their therapy with OAC.
- Specific screening questions allow community pharmacists to detect deficient knowledge in short time and to provide spontaneous verbally unstructured education besides the detection of deficient knowledge when needed.
- The newly developed and validated KODOA-test showed good psychometric properties in Swiss elderly outpatients taking DOAC. The KODOA-test is a reliable and valid questionnaire to assess patient knowledge about DOAC.
- To our knowledge, the KODOA-test is the first validated questionnaire specific for patients taking DOAC and sensitive to change. Therefore, the KODOA-test could be used in clinical trials where associations between knowledge of DOAC and adherence or clinical outcomes are of interest.
- Patient knowledge increases after having received educational counseling either provided spontaneously and in an unstructured manner with the help of the amended PMC or in a structured manner after testing with the KODOA-test.
- Patients show high acceptance and state to be more confident about how to take their anticoagulant agent either after having received educational counselling in an unstructured manner with the help of the amended PMC or in a structured manner after testing with the KODOA-test. More outpatients could be approached for educational counselling about OAC.

Project B: Patient preferences and vitamin B12 deficiency

- The clinical biochemistry of VB12 in T2DM patients with scarce VB12 supply is modified in comparison to nondiabetic patients. This results in higher %AB12 due to reduced VB12 levels. It needs to be clarified whether this effect is due to diabetes itself, metformin treatment and/ or a combination of other heath related situations.
- Assessment of HoloTc seems favorable compared to VB12 to predict hyperhomocysteinemia caused by VB12 deficiency in T2DM patients. This may be a direct consequence of the modified %AB12 in T2DM patients, which strengthens the recommendation to assess VB12 supply in clinical practice by measuring HoloTc.
- After oral and i.m. substitution with VB12, differences in VB12, HoloTc and Hcy levels between groups were higher than expected. Therefore, the hypothesis of non-inferiority of oral treatment had to be rejected. Normalization of HoloTc and MMA was reached by all patients and normalization of VB12 and Hcy by the majority of patients within group O-oral after a one-month treatment. The clinical benefit of exaggerated biomarker response after i.m. treatment within a typical primary care population is questionable. Therapeutic schemes should be chosen with the consideration of mid-term biomarker effects and patient preferences.
- Initial rating in favor of either i.m. or oral therapy can change over time. The majority of patients preferred oral treatment before and after the study, pointing out the need for a high dose oral VB12 preparation in Switzerland.

Project C: Adherence assessment methods

- The German MMAS-8D appears to be a reliable instrument to catch medication adherence in cardiovascular patients. Further, the MMAS-8D is endowed with simplicity and quickness of administration and scoring, which facilitates its use in several pathologies. It may be useful in patients with chronic therapy for detecting non-adherence.
- Combination of subjective and objective adherence measures may help to establish a more precise picture of adherence.

According to the conclusions and findings of this thesis, recommendations for future research and practice are:

Project A: Patient knowledge about oral anticoagulation therapy

- The best way to counsel patients about OAC and association of increased patient knowledge about OAC with adherence and clinical outcomes should be assessed in further studies. **Project D** provides future researcher with a study proposal to investigate associations of increased patient knowledge about OAC and adherence.
- Patient opinions on counselling about OAC and acquisition of knowledge about barriers and facilitators for patient-centred counselling should be of interest in further studies in order to ameliorate educational counselling in primary care setting.
- Health care professionals (HCP) in primary care should screen for deficient knowledge and provide educational counselling about OAC actively. A patients whole therapy and daily experiences have to be included in counselling in order to achieve patient-centred counselling.
- In order to ensure continuous care in OAC patients, it may be helpful to provide different HCP with standardized screening questions and educational manuals about OAC counselling. Remuneration of counselling might increase implementation of such service in daily practise.

Project B: Patient preferences and vitamin B12 deficiency

- Assessment of HoloTc seems more favourable than VB12 to identify VB12 deficient patients. If these findings are restricted to T2DM patients, should be assessed in further studies.
- The impact of T2DM, metformin use and other factors (e.g. age, duration of VB12 deficiency) on VB12 associated biomarkers should be investigated in further studies.
- Optimal injection interval for i.m. hydroxocobalamine is still to be defined. Weekly admisnistration to guidelines lead to exaggerated biomarker response in non-anemic patients. Consequently, lower injection frequency is very likely to be equivalent and thus make treatment for patients more convenient and thereby influencing patient preferences.
- In practice, patient preferences should be assessed routinely before treatment initiation, across various diseases where equivalent treatment options exist. Repeated re-evaluation of patient preferences should be integrated in delivering continuous care because preferences might change over time.

Project C: Adherence assessment methods

- In practice, community pharmacists should screen for non-adherence by combining different methods such as MPR from pharmacy refill data and subjective questions.
- The collaboration with IT specialists to integrate non-adherence alerts from refill data within pharmacy software could support community pharmacists when screening for non-adherence in daily practice.

4 General introduction

4.1 Adherence

Adherence is defined as “the extent to which a person's behavior - taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider” [1]**.** The terms “concordance” and “compliance” are often used as synonyms for adherence. Both are related to the intake of medicine, but they impose different views on the relationship between the patient and the health care professional [2]. “Concordance” describes the agreement between the prescriber and patient in which the beliefs and preferences of the patient have been taken into consideration on the purpose and use of the medication. The term “compliance” is the original term and refers to the extent to which the patient follows the recommendations of the prescriber [2]. Recently a new taxonomy for describing and defining adherence to medications has been published that further divides the process into three quantifiable phases: “initiation”, “implementation” and “discontinuation” [3]. “Initiation” describes the intake of the first dose of a prescribed medication, “implementation” the extent to which a patient’s actual dosing corresponds to the prescribed dosing regimen, from initiation until the last dose and “discontinuation” stopping the intake of the prescribed medication, for whatever reason(s). Additionally, the term “persistence” was introduced as length of time between initiation and the last dose, which immediately precedes discontinuation [2, 3]. Persistence to treatment is of particular interest in chronic diseases with long-term therapy such as oral anticoagulation therapy (OAC) or vitamin B_{12} (VB12) substitution.
Level of adherence to medication varies greatly and is related to treatment, patient and /or health care provider [2]. The World Health Organisation (WHO) stated in 2003 that adherence to long-term therapies in the general population is around 50% in developed countries [4]. A meta-analysis of 569 studies in various settings and conditions reported average non-adherence rate of 24.8% [5].

Non-adherence to medication is a complex, common healthcare problem and can be distinguished in unintentional and intentional non-adherence [2]. Unintentional non-adherence can be considered as an accidental or passive process. The patient does not take the medication as prescribed for example due to forgetfulness or not knowing how to use the medicines or other factors, such as carelessness [2, 6]. Intentional non-adherence reflects the active decision of the patient not to take the medication as prescribed. This is a rational process where patient beliefs

and concerns are important factors influencing the motivation to take the medication [2]. Factors affecting intentional non-adherence are complex and can be related to adverse effects, cost, patient preferences, disagreement of patients with the need for treatment, or communication issues between patient and health care professionals (HCP) among others [7-14]. It has been shown that poor medication adherence may cause toxicity or lack of efficacy [15], disease progression, lower quality of life, drug resistance, medication waste and hospital admission what results in costs of approximately 100 billion a year in the United states [16-19]. Since 2003, the WHO has focused on improvement of medication adherence because of the above mentioned negative outcomes of non-adherence [4]. Therefore, detection of non-adherence and interventions aiming at improving adherence are critically important.

4.1.1. Assessment of adherence

Adherence assessment methods can be broken down into direct and indirect methods. Each method has advantages and disadvantages [18]. The quality of different adherence measurements was assessed in a recent review [20]. In brief, the authors concluded that composite measures are important to establish a detailed picture of adherence. The following subchapters look at a number of different adherence assessment methods that were used within this thesis.

4.1.1.1 Morisky Medication Adherence Scale (MMAS)

Patient self-reports or questionnaires are the most useful indirect methods in clinical settings to assess adherence. This method is simple and inexpensive. However, self-reported questionnaires are subjective and thus susceptible to errors with increases in time between visits. They can easily be distorted by the patient [18].

Among self-reported questionnaires, the Morisky, Green and Levine Medication Adherence Scale [21] is one of the most widely used scale to measure self-reported adherence [22], mainly because of the simplicity of its administration and scoring. It consists of 4 yes/no questions. Because of its poor psychometric properties and its limited value for identifying non-adherent patients to cardiovascular medication [23], the first scale was refined and expanded with 4 further items addressing the circumstances surrounding adherence behaviour. The new 8-item Morisky Medication Adherence Scale (MMAS-8) has demonstrated high internal consistency and good sensitivity and specificity, it is valid and reliable [24]. The questionnaire was shown to be an

effective screening tool in clinical practice to identify non-adherent patients at risk of uncontrolled blood pressure [25]. The MMAS-8 has been translated into more than 50 languages, e.g. French, Malay, Portuguese and Thai [26-29]. Parts of the MMAS-8 have been translated in German and used in specific investigations or larger trials, but the German scale was never validated. Because of the foreseeable use of the MMAS-8 as an adherence measurement and assessment tool in German speaking countries including Switzerland, this thesis focused on a German version of the MMAS-8, the MMAS-8D (Deutsch).

4.1.1.2 Electronic monitoring

From all available indirect adherence assessment methods, the electronic monitoring represents the most objective measure and is recommended as the method of choice in research on adherence [30]. Electronic monitoring allows tracking patterns of medication intake precisely and results are easily quantified. Electronic monitoring can be used to provide feedback based on recorded data. Elevated costs and the necessity of follow-up visits for the downloading of data from devices represent the major disadvantages of this method. Additionally, electronic monitoring systems do not document whether the patient actually ingested the correct drug or correct dose. Therefore, misuse of the device can lead to false positive or false negative results. Finally, a potential bias might occur by reinforcing medication intake through simple observation (Hawthorne effect). When bottles or punch cards are used, a device-specific limitation to certain dosage forms can occur [18, 31].

Up to now, electronic monitoring of one medication was feasible using devices such as the MEMS® caps (Medication Event Monitoring System). In several studies using these electronic caps, discussing the adherence profiles with the patients had a significant impact on patient outcome, mainly through a shared decision of the follow-up strategy [32]. However, only one single medicine was monitored and the derived intervention focused on that specific medicine. Therefore, a new technology to monitor adherence of polypharmacy was developed. The Electronic Monitoring System (POEMS) technology can be used to assess adherence to multiple medication. In brief, POEMS consists of a polymer film with imprinted electronic components that measure the electrical resistance and record the time of its changes when a loop is broken i.e., when a cavity is emptied. The patient's entire oral solid medication is filled in a disposable multidrug punch card with 7x4 cavities, equipped with the film on its backside [33].

4.1.1.3 Rates of prescription refills

Rates of refilling prescriptions are objective, indirect and accurate adherence measures, provided that refills are measured at several points in time. Prescription refills are not equivalent to ingestion of medication and require a closed pharmacy system [18]. Measures reported from secondary database calculate the highest possible level of medication consumption over a particular period. Numerous measures for calculating adherence to one medication from dispensing data records exist, but the nomenclature is inconsistent and computations may vary for similar terms. Recently, a new measure for calculating adherence to polypharmacy has been introduced as Daily Patient Possession Ratio (DPPR) [34].
Within this thesis, the Medication Possession Ratio (MPR) was applied. The MPR is the most commonly used measure for calculating adherence to one medication from dispensing data records. It is calculated by dividing the days' supply of a medication dispensed by the number of days in the time interval of interest [35].

4.1.1.4 Biomarkers

Measurement of a biological marker in blood is a direct, objective method to assess adherence and is often used in clinical trials. Measurement of biomarkers is expensive, burdensome to the HCP and patients, might be influenced by other biological parameters and patient behaviors. It requires expensive quantitative assays [18, 31].

4.1.2 The Polymedication Check – Pharmacy led adherence counselling in Swiss primary care

The Polymedication Check (PMC) was introduced in Switzerland in 2010 as an intermediate medication review for primary care [36]. Comparable pharmacy-led services are available in other countries such as Australia, Canada, the United States of America, the United Kingdom, and New Zealand [37-40]. The PMC allows the community pharmacist to address adherence issues, drug-related problems and to provide direct interventions such as implementation of weekly pill organizer for better medicines management [36]. The PMC is a reimbursed cognitive service and it is based on the Medicines Use Review (MUR) from the United Kingdom [41]. Community pharmacists routinely deliver this service independently from the prescriber for patients taking ≥ 4 prescribed drugs over ≥ 3 months [36]. The PMC takes place in a separated consultation area ensuring privacy in the community pharmacy and lasts about 30 minutes [36]. It can be performed

ad hoc or upon appointment. A recent evaluation of the PMC showed a consistent trend for improved adherence rates in patients treated with antiplatelet drugs after receiving a PMC, however without reaching a significant level [36].

4.1.3 Interventions to improve adherence

To counteract intentional non-adherence, the exploration of the associated factors and patient counselling appear to be important. Interventions should address patients concerns, include motivational interviewing and patient education to increase knowledge about disease and its treatment. To reduce unintentional non-adherence, strategies such as reminder systems, the implementation of medication intake in daily routine or the simplification of medication regimes might be helpful. Thus, there is a need of patient tailored interventions to improve adherence [2]. In general, interventions to improve adherence can be divided into behavioural, technical, educational, and multi-faceted methods [42]. Behavioural interventions usually provide feedback, reminders or rewards to patients. Reduction of regimen complexity and use of fixed-dose regimen are examples for technical interventions. Educational interventions include patient education, provided to individuals or in group sessions using verbal, audio-visual or written material. Effectiveness of multi-faceted approaches using combinations of different intervention types has been demonstrated in long-term situations [43].

A recent Cochrane review on interventions to enhance adherence [44] found that current methods of improving medication adherence for general chronic diseases are mostly complex and evidence of their effects remains low. A supplementary analysis of the Cochrane database assessed congruence between adherence-related patient characteristics and the adherence interventions. The authors concluded that including non-adherent patients was associated with effective adherence interventions which in turn were associated with improved clinical outcomes [45].

In conclusion, evidence for the effectiveness of single adherence interventions is weak, while combined interventions seem to improve adherence. Empowering the patient to participate in shared decisions when it comes to the choice of treatment, to take responsibility for self-care, and to seek social support have been reported to show the strongest effects for therapeutic success [46]. First, patient knowledge and preferences about medication need to be assessed and individualized counselling should be offered in order to empower patients to actively participate in treatment decisions. Second, improvement of adherence and in turn clinical outcomes needs the

development of meaningful combined long-term interventions and follow-ups. Finally, validated instruments for subjective and objective adherence measures are needed that enable the detection of improvements in adherence and clinical outcomes.

4.2. Patient knowledge

Patients have to make important health decisions that affect health outcomes. Furthermore, patients can play an important role in protecting their own health and taking appropriate action in acute episodes of ill health, as well as managing chronic illness. In particular, the management of chronic diseases, such as atrial fibrillation, require a high level of self-care skills that are determined by patient health literacy.

Health is strongly associated with health literacy and other influencing factors such as age, education level, income, race, and employment status [47]. Although importance of health literacy is increasingly recognised, there is no consensus about its definition [48] and different definitions in the context of pharmacy and medications have been recently described, such as “medication literacy” [49]. Overall, health literacy can be described as the people capacity to manage their health [50]. The WHO has adopted a definition of health literacy that reflects a health promotion orientation [51]:

“Health literacy represents the cognitive and social skills which determine the motivation and ability of individuals to gain access to, understand and use information in ways which promote and maintain good health.”

Patient knowledge about medical conditions and treatment regimens is an important aspect of health or medication literacy [52, 53]. In general, the term knowledge can be described as awareness or understanding of facts, information, or skills, that have been acquired through education or experience. Knowledge has been defined as beliefs that are correct and are justified. In addition, a person needs to be certain to be able to know something [54]. Patient medication knowledge - or shortly named in this thesis “patient knowledge” - refers to patient health knowledge related to medications including what is being used, why it is being used as well as instructions and precautions of use of certain medication. Patients with low knowledge about how to manage their illness were found to have low health literacy [55-57]. Therefore, patient counselling about medication and engagement in their own health should be integrated in daily practice [58].

4.2.1 Patient education and counselling

Patient education has been defined as "*a planned learning experience using a combination of methods such as teaching, counselling, and behavior modification techniques which influence patients' knowledge and health behavior*" [59]. Patient education attempts to improve health – or medication literacy - and attitudes that are necessary to change patient behavior [60] and ultimately improves health outcomes [61]. Behavior change depends on different factors, such as patients perceptions of health and illness, as well as effective communication with HCP [62]. It has been demonstrated that informing patients about medication can influence patient outcomes positively mainly when communication is empathic [63]. The patient centered type of communication encourages patients to express their perceptions on treatment, establishes patients and HCP as partners and takes patient emotional and social environments into account. Patient centered communication requires open-ended questions and mutual participation, in contrary to biomedical communication which uses closed-ended questions [63].

Patient counselling can include different aspects in order to help the patient better manage health problems [59], such as adherence counselling or medical counselling. Patient counselling about medication should include a dialog of the advantages and disadvantages of each single drug of a therapy regimen. Information transfer between HCP and patient should include information on the effects of the drug, its dose and the timing of intake as well as an explanation of the meaning and probability of potential adverse effects and interactions [52]. Both, patient education and counselling, involve an interactive process which actively engages patients to participate in their own health [59].

Up to now, however, counselling practice about medication in general practitioners' practices seems to be poorly implemented. Studies reported that between 17% and 30% of physicians give no verbal instructions when medications are prescribed [64] and for almost one third of the cases, the name of the drug – either new or changed - is not mentioned [65]. A more recent study concluded that in general, medical encounters lack depth and although communication skills are now part of most medical curriculums, the concept of patient medication knowledge-building over multiple clinician–patient encounters should be strengthened [66]. Community pharmacists have an important role in patient counselling about medication [67]. Studies investigating counselling practice in community pharmacies show that there is room for improvement. Patient counselling in community pharmacies appeared to be of little importance in daily practice [68-70]. Additionally,

community pharmacists provide little medication-related information at the counter, especially for repeated refills on long-term prescriptions [71] and about half of the patients do not receive any counselling [72]. Furthermore, patient-community pharmacist communication seemed predominantly nonmedical or product-centered, instead of patient-centered [73, 74]. Studies examining patient knowledge about medication from hospital also report significant deficits in patient knowledge of hospital medications [75] and a need for structured medication teaching programs [76]. Therefore, it is not surprising that outpatients lack knowledge about their medication [77]. Suboptimal patient knowledge about high-risk medication, such as OAC, was reported [78]. Lack of knowledge of medication and difficulties in understanding medication information may be related to misapprehension of instructions and/or symptoms, medication errors, low self-care behavior, poor health outcomes, and frequent visits to the emergency department [49].

4.2.2 Assessment of patient knowledge

To determine whether a person possesses knowledge about a certain topic, i.e. medication, simple questions that are representative of the topic should be asked. Items of test instruments used to assess knowledge should not be biased, i.e. influenced by the test participants' characteristics other than knowledge [54]. Patient knowledge can be retrieved orally using structured or semi-structured interviews or with written test forms. The following subchapter focuses on written test forms.

4.2.2.1 Assessment of knowledge deficit with written test forms

Written test forms are the most appropriate method used for the assessment of cognitive knowledge in medical education settings. Two major types of assessment forms can be distinguished: items with selected-response and items with constructed-response formats [79]. Selected-responses can have the forms true and false, or multiple choice. Multiple choice formats are the most appropriate and efficient forms to objectively assess cognitive knowledge [79].
Constructed-response forms require the examinee to produce responses to open-ended questions, or other stimuli such as short and long answer essays. Scoring objectively constructed-response formats is more difficult as with the selected-response form. Nevertheless, some types of assessments such as the evaluation of writing skills require constructed-response forms [79].

4.2.3 Patient knowledge and adherence

While the influence of health literacy and medication knowledge is considered important during the process of health /disease management, adherence to treatment is another important factor. A recent Cochrane review concluded that interventions that provide information or education may improve adherence, clinical outcomes and knowledge when used in combination with other interventions (i.e. counselling as part of pharmacist-delivered packages of care, training of self-management skills), but results are mixed [80].

In the case of OAC, individual studies showed that enhancing patient knowledge about medication and the underlying disease was able to improve long-term adherence [81, 82]. However, according to a recent Cochrane review, there is insufficient evidence to draw definitive conclusion regarding the impact of educational interventions on therapeutic outcomes in patients receiving OAC [60] mostly due to inhomogeneity of the study designs. Thus, educational contents need to be prioritized and educational domains should be standardized [61]. Simple screening tools could be useful for the detection of knowledge gaps in daily practice. Further, standardized validated instruments for the assessment of deficit knowledge are needed to demonstrate the impact of patient education on outcomes in clinical trials. Finally, patient counselling about medication and available therapy options represents the first step to promote shared decision-making and apply evidence-based medicine and patient preferences.

4.3 Patient preferences

Nowadays, a variety of treatment options exist for a single disease. The aim of a specific treatment can be the reduction of mortality or morbidity, the reduction of symptoms, or the improvement of the quality of life. Besides differences in health outcomes (such as for example the duration of life prolongation, side effects), therapy options can differ in other characteristics such as the application form or the costs.

Patient preferences result from unique values (i.e. potential benefits, convenience) and concerns (i.e. potential harms, costs) that are formed by patient experiences, knowledge and reflection. Having preference for a treatment mirrors the patient evaluation of these values and concerns in comparison with an alternative treatment option. For a given disease, different patients may have different preferences. Each patient brings their preference to a clinical encounter that should be integrated in decision making whenever they are to serve the patient [83-86].

Decisions resulting from preferences are personal judgements and involve balancing possible benefits and possible risks of the optional treatments [87]. Patients must be able to understand information, recognize benefits and consequences of various alternatives, question information rationally, and communicate their preference, to have capacity for a particular decision [88]. Besides benefits, risks and costs of a given treatment, practical aspects such as the patient ability to open package of medication, impairments within daily life caused by the medication or access to medication need to be considered [89]. Even though the underlying disease may influence the amount of decision-making patients want [90, 91], patients recognize that they are the best judges of their values when reflecting different options for their health care problem [92]. A method to include patient preferences by HCP is the model of Shared Decision Making [93].

4.3.1 Shared decision-making

In a systematic review, an integrative model of Shared Decision Making (SDM) was proposed and nine essential elements based on 161 definitions were identified [94]:

1. Define /explain the health problem
2. Introduce (treatment) options
3. Discuss pros and cons (benefits/risks/costs)
4. Assess patient values and preferences
5. Discuss patient ability and self-efficacy
6. Present doctor knowledge and make recommendations
7. Check /clarify the patients understanding
8. Make or explicitly postpone decision
9. Arrange follow-up

Within the SDM model, the patient and the HCP share the responsibility to decide on a treatment [95, 96]. The HCP's task is to provide patients with evidence-based medical knowledge, experiences and attitudes while patients disclose their individual values, treatment goals and expectations. Then, a subsequent decision can be made based on evidence-based medicine and patient preferences [97, 98]. Throughout the process, both parties should periodically check the patient ability to follow-up the chosen treatment plan and changes in understanding of facts and perspectives and if needed to provide further clarification [94].

It has been shown that knowledge about patient preferences for a certain disease might lead to better informed decisions in practice and in health policy [84]. A systematic review gave evidence that SDM can be an effective method of reaching a treatment agreement in particular in long-term decisions, in the context of a chronic illness or when the intervention contains follow-up sessions [99]. Few studies exist about concordance between patient preferences and initiated treatment. Standardized interventions might facilitate the exchange of views between patients and health care providers [89]. SDM is particularly recommended for situations with two or more equivalent available treatment options and similar treatment consequences for a patient daily life. The substitution of VB12 in outpatients with VB12 deficiency is one example where the equivalent efficacy of oral and intramuscular application offers for patients both treatment opportunities.

4.3.2 Assessment of patient preferences

Patient preferences concern three areas: the specific health state, the treatment itself and the patient participation, i.e. if a patient wants to be involved in the decision making process [95]. In a rational world, preference for health state are linked to preference for treatment [100]. However, some patients might prefer to avoid for example a major surgery although surgery might be the most effective option to increase lifespan. Therefore, in addition to the preferences, the values on which preferences are based should be assessed. This may especially clarify wrong information and unjustified beliefs. It has been shown that a significant proportion of patients would like to play an active role in decisions concerning their health [101]. Furthermore, patient participation in the decision-making process may be associated with favorable health outcomes [102, 103], even when patients avoided to be part of the decision making [104, 105]. Thus, asking patients about their preferences and values seems advantageous for every patient.
A review about patient preferences in cancer treatment showed that a variety of methods exist to assess patient preferences, such as standard gamble, time to trade off or discrete choice experiment. However, the easiest method to assess preferences is by ranking or rating [84] a given set of alternative treatment options on a scale (for example Likert). The strengths of this approach are its easiness and quickness. Most of the methods ask patients what they would do in a hypothetical situation rather than what they would chose in a real situation [84].

4.3.3 Patient preferences and adherence

It has been recognized that one single guideline does not account for the differences in patient preferences for treatments and health outcomes, suggesting a need for flexible guidelines that might facilitate patient involvement in clinical decision making [106]. A better understanding of patient preferences is pivotal for shared decisions and important for increased adherence and ultimately patient health outcomes [100]. Patient preferences in treatment-related decisions should be elicited and taken into account because patients who felt less empowered with regard to treatment decisions reported lower rates of adherence [107].

4.4 Oral anticoagulants

OAC are used for the prevention and treatment of both venous and selected arterial thrombotic disorders, such as atrial fibrillation (AF) [108]. For many decades, vitamin K antagonists (VKAs) have been the only available OAC despite their many limitations. Therefore, direct oral anticoagulants (DOAC), also called non-vitamin K oral anticoagulants (NOAC) have been developed to overcome VKA limitations. However, therapy with VKA and DOAC entails a high potential for adverse events and strict adherence is needed. Furthermore, the main target population is aged, presents multiple comorbidities and uses polypharmacy. Adherence and persistence to medication regimen increase when patients understand the reasons for the prescription, know potential side effects and know how to handle risky situations. For these reasons, medication review, the identification of safety issues and patient education are important for anticoagulation therapy with VKA and the newer anticoagulants. The following chapters introduce VKA and DOACs that are approved in Switzerland.

4.4.1 Vitamin K antagonists

VKAs (coumarins) used in Switzerland are phenprocoumon (Marcoumar®) and acenocoumarol (Sintrom®). VKA's interfere with the synthesis of proteins important for blood clotting like prothrombin (factor II), factor VII, factor IX and factor X in the liver. In more detail, VKAs interfere with the cyclic interconversion of vitamin K and its 2,3 epoxide (vitamin K epoxide), thereby modulating the g-carboxylation of glutamate residues on the N-terminal regions of these vitamin K-dependent proteins. Therefore, treatment with VKAs results in the hepatic production of partially carboxylated and decarboxylated proteins with reduced coagulant activity [109]. Phenprocoumon is a long-acting agent, with both the R- and S-isomers having elimination half-lives of 5.5 days. Both are metabolized by CYP2C9. Acenocoumarol also exists as isomer. R-acenocoumarol has an elimination half-life of 9 hours, is primarily metabolized by CYP2C9 and CYP2C19, and is more potent than S-acenocoumarol which has an elimination half-life of 0.5 h and is primarily metabolized by CYP2C9 [109].

All VKA's are highly susceptible to drug-drug interactions, have drug-food interactions and a narrow therapeutic window. Therefore, anticoagulation with VKAs has to be monitored regularly through the assessment of International Normalized Ratio (INR) [109]. The INR is a standardized method to monitor the extrinsic pathway of the coagulation cascade. Its value indicates how much longer the blood needs to coagulate compared to physiological situations. The therapeutic range

of the INR value is usually between 2 and 3.5. Regular monitoring with dose adjustment is needed to ensure effective and safe anticoagulation [110] . It was shown that best therapeutic effects are achieved if the INR is in the therapeutic range at least 70% of time [111]. The effect of the anticoagulation starts two to three days after therapy-initiation and the full effect is achieved after five to seven days. This implies that in case of a desired rapid anticoagulation effect the bridging with a low molecular heparin is necessary at the initiation of treatment [110] .

4.4.2 Direct oral anticoagulants

In Switzerland, so far (September 2017) four different DOACs have been approved: Rivaroxaban (Xarelto®), apixaban (Eliquis®), edoxaban (Lixiana®) and dabigatran (Pradaxa®).
Rivaroxaban, apixaban and edoxaban are selective and competitive reversible factor Xa inhibitors. Factor Xa activity is highly dependent on the concentration of the drug and the onset of action is rapid. The activation of factor X to factor Xa via extrinsic and intrinsic coagulation pathways plays an important role in the coagulation cascade and leads to the activation of prothrombin to thrombin. The inhibition of factor Xa leads to the prevention of thrombin formation. Factor Xa inhibitors has no effects on platelet aggregation induced by collagen, adenosine diphosphate, or thrombin [109].
Dabigatran is a concentration dependent, competitive, highly selective and reversible direct thrombin inhibitor. Because the dabigatran molecule is highly polar and lipophobic, it is not absorbed and its oral availability required the synthesis of an absorbable prodrug, dabigatran etexilate. Dabigatran prevents the conversion of fibrinogen to fibrin and thereby prevents thrombin-induced platelet aggregation but not platelet aggregation by arachidonic acid, collagen, or adenosine diphosphate [109].
DOACs are taken once or twice daily, they all have a short elimination half-life and have similar pharmacokinetics properties (Table 1).

Table 1: Pharmacokinetic properties and interactions of rivaroxaban, apixaban, edoxaban and dabigatran adapted from [108, 112, 113].

	Rivaroxaban	Apixaban	Edoxaban	Dabigatran
Dosing	Once (or twice) daily	Twice daily	Once daily	Twice daily
Prodrug	No	No	No	Yes
Bioavailability	66-100%*	52%	62%	3-7%
Peak plasma concentration	2-4 h	3-4 h	1-2 h	0.5-2 h
Clearance non-renal / renal	66% / 33%	75% / 25%	50% / 50%	20% / 80%
Liver metabolism via CYP 3A4	Yes	Yes	Yes	No
Elimination half life	5-9 h (young) 11-13 h (elderly)	12 h	10-14 h	12-17 h
Drug interactions	CYP 3A4 (P-gp)	CYP 3A4 (P-gp)	P-gp-Inhibitors (CYP 3A4)	PPI,P-gp-inhibitors

*Dependent on intake without or with food
P-gp= P-glycoprotein
PPI= Proton pump inhibitors

4.5 Vitamin B12

VB12, is a water-soluble vitamin and essential for DNA-, fatty acid- and hem synthesis [114]. VB12 is also called cobalamin and refers to a variety of structurally related compounds. Cobalamins contain a central cobalt ion coordinated to four nitrogen atoms donated by the tetrapyrrolic corrin-ring system. The axial ligand on the lower surface of the corrinring is the nucleotide base dimethylbenzimidazole. The second axial ligand lies on the upper surface of the ring. Different ligands can coordinate to the cobalt ion. The ligand may be a cyano-, hydroxyl- alkyl group or 5- deoxyadenosyl [115] (Figure 1). VB12 is synthesized by some bacteria species and has to be ingested from food. Sources of VB12 include mainly animal products such as liver, meat, fish, eggs milk and cheese [116, 117]. A typical Western diet contributes 3–30 µg of cobalamin per day toward the estimated daily requirement of 2,4 µg that is recommended by DACH Liga for adults [118, 119].

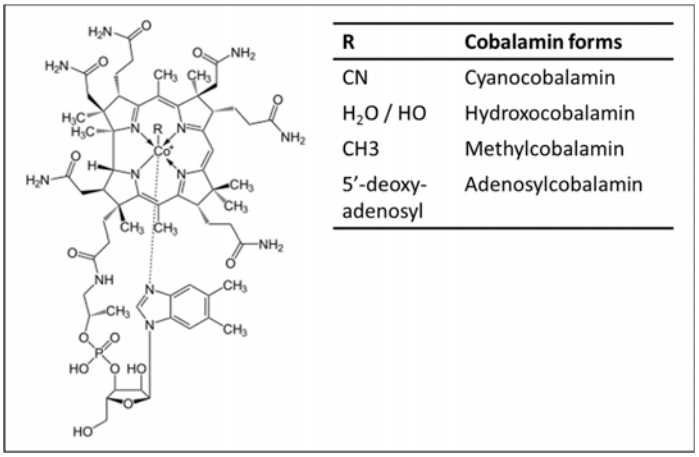


Figure 1: Vitamin B12 forms. Adapted from: Obeid R et al. [117].

After ingestion, pepsin and hydrochloric acid release VB12 in the stomach from animal proteins. A central role for the absorption of VB12 plays the Intrinsic Factor. The Intrinsic Factor is a glycoprotein that is synthesized in the parietal cells of the stomach. Within the small intestine, VB12 is bound by Intrinsic Factor leading to receptor-mediated endocytosis. It is supposed that around 1% of VB12 is absorbed by passive diffusion. Within the blood circulation, VB12 is bound to transcobalamine, called holotranscobalamine (HoloTc). HoloTc is the biologic active form available for cell [120, 121] . VB12 is stored mainly in the liver and in case of abstinence, storage is depleted within 2 - 5 years. Then a VB12 deficiency occurs.

4.5.1 Detection of vitamin B12 deficiency

Biochemically, VB12 deficiency is characterized by subnormal to borderline VB12 values in serum (<148-221 pmol/l) [122]. HoloTc is the bioactive form of VB12 and makes up to 20% of the total VB12 concentration in the human body [123]. It has been discussed as a more specific and sensitive marker of VB12 deficiency [124-126]. Broad ranges of cut-off points for HoloTc have been described <20 – 50pmol/l [127]. Functional VB12 deficiency is characterized by elevated homocysteine (Hcy) and/or methylmalonic acid (MMA) [122]. However, it is known that clinical biochemistry of VB12 is influenced by different health states. One example of altered VB12 metabolism is type 2 diabetes and its treatment [128, 129] (Figure 2).

Figure 2: Relationship between Diabetes, Metformin treatment, health situation and VB12 status.

Further laboratory findings are hematological abnormalities such as macrocytosis, pancytopenia and hypersegmented neutrophils (Figure 3). Hematological changes can be found in the more severe cases, while biochemical findings go in parallel with less specific clinical manifestations of VB12 deficiency. However, no clear-cut limits exist for the prediction of symptoms [130]. Subclinical VB12 deficiency occurs and is found in up to 10-25% of the aged population. Treatment of these patients is common, even though the long-term benefits of such treatment are unclear [122].

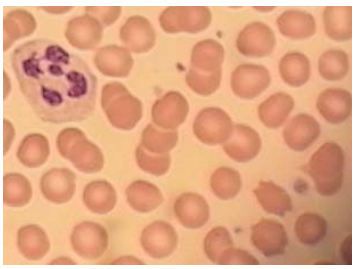


Figure 3: Hypersegmented neutrophil.

4.5.2 Treatment of vitamin B12 deficiency

The treatment of VB12 deficiency consists of VB12 supplementation, which can be performed either orally or by injections. In Switzerland, VB12 supplementation is predominantly performed with i.m. injections of VB12 [131], which are usually painful. In Switzerland, only combination preparations for oral substitution are available containing different doses of cyano- or hydroxocobalamine (Table 2). Oral treatment with VB12 may be superior to i.m. injections in terms of patient acceptance and cost-effectiveness [132]. Patient preferences in treatment-related decisions should be elicited and taken into account, because patients who feel less empowered with regard to treatment decisions reported lower rates of adherence [107].

Table 2: Examples for VB12 containing products in Switzerland.

	Dose (mg)	mono (M) / combination products (K)	Rx/ OTC	Application
Products containing cyanocobalamine				
Supradyn Energy	0.003	K	OTC	oral
Berocca ®	0.01	K	OTC	oral
Becozym forte ®	0.01	K	OTC	oral
Vitasprint ®	0.5	K	OTC	oral
Benexol ®	1	K	Rx	oral
Vitarubin superconc®	1	M	Rx	i.m, (s.c./i.v*)
Products containing hydroxocobalamine				
Biovigor®	0.5	K	OTC	oral
BIO-LOGOS ®	0.5	K	Rx	oral
Vitarubin Depot®	1	M	Rx	i.m, (i.v*)

i.m. = intramuscular
s.c. = subcutaneous
i.v. = intravenous
Slow intravenous application possible, but not recommended [133]

5 Thesis overview

The goal of this thesis was to assess knowledge of oral anticoagulation therapy and preferences for VB12 in outpatients, and to develop an educational program for outpatients on DOAC. The thesis approaches this goal in four parts:

5.1 Project A: Patient knowledge of oral anticoagulation therapy

Community pharmacists are one of the last HCP patients see before they take their medicines. Therefore, pharmacists play an important role in counselling about adherence and about medicines. **Study A-1** aimed at assessing outpatients knowledge of OAC in Swiss community pharmacies. Within this study, the basic PMC was amended with specific open-ended questions on OAC. The impact of the amended PMC on basic knowledge of OAC was assessed in an observational study with patients treated with VKA or DOACs. Knowledge gaps regarding OAC therapy were frequently detected and resulted in pharmaceutical intervention improving patient knowledge. Patients on DOAC had more knowledge gaps compared to VKA patients. Up to now, no questionnaire assessing patient DOAC knowledge was psychometrically validated. Therefore, the aim of the second study was to develop and validate a questionnaire to self-assess knowledge of DOAC that can be used in clinical trials (**Study A-2**). An item pool to assess knowledge of DOACs was retrieved from a systematic literature review and reduction of items was achieved with a focus group discussion. The newly developed questionnaire was then validated in outpatients with a prescription for DOAC.

Table 3: Overview of the studies of Project A.

Project A	
Study A-1	**Intermediate medication review focusing on oral anticoagulation therapy enhances patient's medication literacy – an observational study in Swiss community pharmacies** (research report) ➢ To detect knowledge gaps about OAC in outpatients ➢ To observe the counselling process of community pharmacists with the help of the basic PMC amended with specific questions on OAC ➢ To assess the impact of the amended PMC on patient knowledge of OAC
Study A-2	**Development and validation of a tool to assess knowledge of DOAC** (published in: Drug Healthc Patient Saf. 2018 Jul 20;10:69-77. doi: 10.2147/DHPS.S152954. eCollection 2018.[134]) ➢ To develop a questionnaire to self-assess patient knowledge of DOAC ➢ To test acceptability, feasibility, reliability, face and content validity of the new questionnaire

Project B: Patient preferences and vitamin B12 deficiency

VB12 deficiency is relatively common, especially in elderly. Recently, an increased frequency of VB12 deficiency among T2DM patients has been documented. The clinical biochemistry of VB12 is influenced by diabetes and its treatment. Systematic observations in clinical trials as well as biochemical studies in animals raised questions on possible interactions between diabetes, metformin treatment and VB12 metabolism. **Study B-1** aimed at assessing whether serum VB12 or HoloTc is more suitable to detect VB12 deficiency in T2DM patients. Furthermore, differences in VB12 associated biomarkers were analysed i) among diabetic outpatients with and without metformin use and ii) in comparison to an external non-diabetic reference group with low VB12 (<200pmol/L).Because VB12 deficiency is a reversible cause of demyelinating nervous system disease and bone marrow failure, its early detection and treatment of deficient patients are important. The treatment of VB12 deficiency consists of VB12 supplementation which can be performed either orally or by intramuscular (i.m.) injections. In Switzerland, VB12 supplementation is predominantly performed with i.m. injections of VB12, which are usually painful. No high-dose VB12 oral mono-preparation is currently available, despite evidence of its effectiveness. Moreover, when equally effective treatment options exist, patient preferences need to be

taken into account. Patients who felt less empowered with regard to treatment decisions reported lower rates of adherence. Finally, a better understanding of patient preferences and values for making choices is fundamental to achieve shared decision making and ultimately improve adherence. Therefore, **Study B-2** aimed at assessing patient preferences to oral and i.m. VB12 substitution. Furthermore, **Study B-2** aimed to prove non-inferiority of oral treatment compared to i.m. VB12 substitution. **Study B-3** aimed to assess patient preferences towards oral and parenteral treatment in various diseases. A literature review retrieved 13 research articles with focus on patient preferences.

Table 4: Overview of the studies of Project B.

Project B	
Study B-1	**Impact of type 2 diabetes and metformin use on Vitamin B12 associated biomarkers - an observational study** (published in Exp Clin Endocrinol Diabetes. 2018 Jun;126(6):394-400. doi: 10.1055/s-0043-120760. Epub 2018 Feb 2. [135]) ➢ To assess the effect of metformin treatment on VB12 status as reflected by total VB12 and HoloTc in T2DM patients. In particular, the the biologically active fraction %AB12 (=HoloTc/VB12*100) in T2DM patients with and without metformin treatment was compared. ➢ To investigate the impact of diabetes itself on VB12 associated biomarkers at low VB12 levels in patients with diabetes, in comparison to an external reference group of non-diabetic patients. ➢ To assess the suitability of VB12 and HoloTc to represent VB12 supply in T2DM patients
Study B-2	**Early Biomarker Response and Patient Preferences to oral and intramuscular Vitamin B12 Substitution in Primary Care: A Randomized Parallel Group Trial** (publication in Swiss Med Wkly. 2017 Apr 19;147:w14421. doi: smw.2017.14421. eCollection 2017 Apr 19. [136]) ➢ To compare patient preferences for oral versus parenteral treatment before substitution with VB12 with preferences after a one-month therapy. ➢ To assess early biomarker response to the supplementation with oral or i.m. VB12 treatment in outpatients.
Study B-3	**B 3 Oral versus parenteral route of application: The patients' perspective** (research report [137]) ➢ To assess patient preferences towards oral and parenteral treatment in various diseases.

Project C: Adherence assessment methods

Considering that interventions aimed at optimizing adherence will be more effective if they are tailored to patient´s needs, HCPs will need tools to measure adherence. Among self-reported questionnaires, the Morisky Medication Adherence Scale is one of the most widely used. However, to date no German version is available. Therefore, **Study C-1** aimed to translate the MMAS-8 and psychometrically validate it in cardiovascular patients. In Switzerland, the PMC, an intermediate medication review focusing on adherence issues, is available since 2010. The PMC contains one single adherence question from [138]: "Do you sometimes forget to take your medication?" to screen for non-adherence. It is known that subjective measures such as questionnaires are easily distorted by the patient. Therefore, a pilot study in DOAC treated patients aimed to evaluate whether the affirmative answer to the subjective PMC question coincides with an objective adherence measure. The MPR calculated from pharmacy refill data served as comparator **(Study C-2**).

Table 5: Overview of the studies of Project C.

Project C	
Study C-1	**The 8-item Morisky Medication Adherence Scale translated in German and validated against objective and subjective polypharmacy adherence measures in cardiovascular patients.** (Second author, published in J Eval Clin Pract. 2015 Apr;21(2):271-7. doi: 10.1111/jep.12303. Epub 2015 Jan 6. [139]) ➢ To translate and validate the 8-item Morisky Medication Adherence Scale in German in cardiovascular patients.
Study C-2	**Medication possession ratio may detect half of the self-declared non-adherent patients to direct oral anticoagulation treatment – A pilot study** (research report [140]) ➢ To assess whether the affirmative answer to the PMC question "Do you sometimes forget to take your medication?" coincides with a MPR <90% (non-adherence) in DOAC treated patients.

Project D

Finally, **Study D** aimed to develop a tailored and stepwise educational program on adherence to DOAC therapy in Switzerland. This study design allows to investigate the impact of the intervention on subjective (questionnaire based) and objective (electronically monitored) adherence and to assess patient satisfaction with an educational tailored and stepwise program.

Table 6: Overview of Project D.

Project D	
Study D	**Impact of a tailored and stepwise educational program on adherence to rivaroxaban therapy in Switzerland – adaptable to other European countries such as Germany or France** (Research protocol) ➢ To develop a stepwise educational program on adherence for patients on DOAC and especially on rivaroxaban using feedback from electronic monitoring. ➢ To investigate the impact of the intervention on subjective (questionnaire based) and objective (electronically monitored) adherence. ➢ To assess patient satisfaction with an educational tailored and stepwise program on anticoagulation therapy.

6 Project A: Patient knowledge about oral anticoagulation

6.1 Intermediate medication review focusing on oral anticoagulation therapy enhances patient's medication literacy – an observational study in Swiss community pharmacies [A-1]

Corina Metaxas, Albert Valerie, Habegger Susanne, Markus Messerli, Kurt E. Hersberger, Isabelle Arnet

Department of Pharmaceutical Sciences, Pharmaceutical Care Research Group, University of Basel, Pharmazentrum, Klingelbergstrasse 50, 4056 Basel, Switzerland

Research report

Abstract

Introduction

Oral anticoagulation therapy (OAC) is often prescribed to elderly patients with polypharmacy (>3 different medications). High adherence to OAC is needed for optimal therapeutic outcomes. Since 2010, Swiss community pharmacists can deliver an intermediate medication review, the Polymedication Check (PMC) that focuses on adherence and handling problems. The pertinence of the delivered information through the PMC and its impact on patient knowledge has never been investigated. We amended the basic PMC with open-ended questions on OAC and evaluated general knowledge of outpatients taking vitamin K antagonists (VKA) or direct oral anticoagulants (DOAC).

Methods

Based on previous studies, an amended PMC with focus on knowledge of OAC was developed. Fifth-year pharmacy students documented one amended PMC with OAC patients during their internship in community pharmacy. They documented knowledge gaps, pharmacists-led interventions and patients' satisfaction with the amended PMC.

Results

A total of 81 patients (61.7% VKA, 38.3% DOAC) received an amended PMC. Half of the patients (50.6%) did not know how to proceed in case of a missed dose. Percentage of patients with at least one knowledge gap decreased from 65.4% to 23.8% after spontaneous educational intervention ($p<0.001$). Most patients (98.6%) were satisfied with the counseling provided by the pharmacists.

Conclusion

The majority of OAC patients shows knowledge gaps that could be detected by community pharmacist through the amended PMC. Although spontaneous and unstructured, the provision of tailored education increased patients' medication literacy. Thus, a simple screening with open-ended questions enables community pharmacists to easily counsel OAC patients.

Keywords: medication literacy, oral anticoagulants, patient knowledge, medication review

1. Introduction

Oral anticoagulation therapy (OAC) is prescribed for the prevention and therapy of thromboembolic diseases [141-143] with either vitamin K antagonists (VKA) or direct oral anticoagulants (DOAC), also called non-vitamin K antagonist oral anticoagulants (NOAC). The chronic nature of anticoagulant treatment and the inherent bleeding risk increase the challenge of treatment for both types of OACs. DOACs were developed predominantly to overcome the practical difficulties associated with VKAs (i.e. frequent dosage-adjustments, drug-drug, drug-food interactions)[144]. However, strict intake time i.e., a high adherence rate is needed to achieve optimal therapeutic outcome with VKA and DOAC [145]. Non-adherence may reach 32% in patients with the VKA warfarin [146] and similar adherence levels can be assumed with DOACs [147] since both agents have the same target population that is aged, presents multiple co-morbidities and uses polypharmacy [148]. Non-adherence can be intentional or non-intentional [2]. Unintentional non-adherence can be considered as an accidental process. The patient does not take the medication as prescribed due to e.g., forgetfulness or not knowing how to use the medicines. Unintentional non-adherence can be decreased by the addition of a reminder system (i.e., weekly pill organizer) [149]. Intentional non-adherence reflects the active decision of the patient not to take the medication as prescribed. This is a beliefs-based process that influences the motivation to take the medication. Patient counseling and education about medicines may improve intentional adherence [2, 150]. Finally, interventions aimed to increase adherence are likely to succeed if the entire medication is taken into account. Therefore, the performance of a medication review represents an essential first step in any adherence counseling [36].

1.1 Polymedication Check

The Polymedication Check (PMC) was introduced in Switzerland in 2010 as an intermediate medication review for primary care [36]. Comparable pharmacy-led services are available in several other countries such as Australia, Canada, the United States of America, the United Kingdom, and New Zealand[37-40]. The PMC allows the community pharmacist to address adherence issues, drug-related problems and provide direct interventions i.e. implementation of weekly pill organizer independently from the prescriber [36]. The PMC is a reimbursed cognitive service and it is based on the Medicines Use Review (MUR) from the United Kingdom [41]. The pertinence of the delivered information through the PMC and its impact on patient knowledge has never been investigated until now.

1.2 Patient education

Different definitions for health literacy in the context of pharmacy and medications have recently been described, such as “medication literacy” [49]. Patient education attempts to improve medication literacy and attitudes that are necessary to change patient behavior [60] and ultimately to improve health outcomes [61]. Difficulties in understanding medication information may be related to misapprehension of instructions and/or symptoms, medication errors, low self-care behavior, poor health outcomes, and frequent visits to the emergency department [49].

It has been demonstrated that informing patients about medication can influence patient outcomes positively mainly when communication is empathic[63]. A patient-centered communication establishes patients and health care providers (HCP) as partners, takes patients’ emotional and social environments into account and requires open-ended questions to encourage patients to express their perceptions on treatment [63]. Few studies showed that enhancing patient knowledge about OACs and the underlying disease were able to improve long-term adherence [81, 82]. However, according to a recent Cochrane review, there is insufficient evidence to draw definitive conclusion regarding the impact of educational interventions on therapeutic outcomes in patients receiving OAC [60] mostly due to inhomogeneity of study designs. Thus, educational contents need to be prioritized and educational domains should be standardized [61]. Therefore, simple screening tools could be useful for the detection of knowledge gaps.

Usually, community pharmacists are the last HCP patients see before they take their medication. In Switzerland, physicians hand out prescriptions for chronic diseases that are valid for up to one year. Therefore, pharmacists are in a central position to assess a patient’s medication literacy, counsel and provide a follow-up beside the delivery of the medication. The ability of detecting knowledge gaps in patients with chronic treatments such as OAC could help pharmacists or other HCPs to enhance adherence. We amended the basic PMC with a semi-structured questionnaire containing open-ended questions on OAC resulting in a new protocol for a specific MR with OAC patients.

1.3 Aim of the study

We aimed at assessing the impact of the amended PMC on OAC knowledge of outpatients taking VKAs or NOACs.

2. Methods

2.1 Trial design

A cross-sectional study was initiated by the Pharmaceutical Care Research Group (PCRG) of the University of Basel. Swiss community pharmacies that employed pharmacy students in their final year (internship) served as recruiting places. The study was conducted in accordance with the Declaration of Helsinki and has been registered at ClinicalTrials.gov ID NCT02703727. The study was approved by the regional ethic committee (EKNZ 50/12). All patients gave written informed consent.

2.2 Data collection

Fifth year pharmacy students were trained on OAC and PMC during plenary lectures of the regular curriculum at the University of Basel. A descriptive manual and an online training including one video, which described the study procedure and provided instructions for the correct use of amended PMC and the follow-up interview, were available for the students

Community pharmacists were instructed to perform a basic PMC (A) with an orally anticoagulated patient in the pharmacy and (B) to add the newly developed semi-structured interview immediately after the basic PMC. Students observed the patient-pharmacist-interaction and documented all the pharmacist-led interventions on provided standardized protocols. Two weeks later, students called the patients by phone and performed a follow-up interview (C).

2.2.1 Basic PMC (A)

The basic PMC contains several items to be checked for every single medication such as knowledge about the therapy: “know how to take the medication” (item 2) and “know why to take the medication” (item 3) (Table 1). Item 1 concerns the name and dosage of the product. It is rarely asked because name and dosage are mostly extracted in advance from the pharmacy software. The PMC does not specify how the questions should be asked. According to the patient’s response, the pharmacist ticks the appropriate box in the report. After gathering information the pharmacist delivers targeted information in an unstructured manner [72].

2.2.2 Development of the amended PMC on OAC (B)

Thirteen items from a French publication about the evaluation of a pharmaceutical interview in an anticoagulation clinic [151] were translated into German (CM). Readability and comprehension were approved by three German native speaking pharmacists (MM, SH, KH). Five items were not specific for OAC (n=2) or did not concern knowledge about OAC (n=3) and were therefore excluded. The remaining eight items delineating knowledge were formulated as open-ended questions (Table 1). Asking these eight questions in form of a semi-structured interview placed at the very end of a basic PMC was supposed to take about 10 minutes.

Table 1: Questions asked in the basic PMC (A), the following semi-structured interview (B) and/or the follow-up interview (C).

Item	Content	Asked in
2	"knows how"	A , B , C
3	"knows why"	A , B , C
4	"What happens in case of underdosage"	B , C
5	"What happens in case of overdosage"	B , C
6	"What to do in case of a missed dose"	B , C
7	**"**How long to take the OAC"	B, C
8	"Why to inform HCPs about having an OAC therapy**"**	B , C
9	"I would recommend this service to other patients"	C
10	"The pharmacist was able to answer all my questions"	C
11	"I am more confident about how to take my OAC"	C
12	"It is easier to take my OAC as prescribed"	C
13	"I have less concerns about my therapy with OAC"	C

2.2.3 Development of the follow-up interview (C)

The same eight questions delineating knowledge were completed with five additional items about patient satisfaction using 5-point-Likert scales retrieved from a prior study [36] (see Table 1).

2.2.4 Pilot study

Comprehension of the amended PMC, usability of the standardized protocol for documentation of interventions by students and feasibility of the study design was tested with 91 fifth year pharmacy students of a prior study course (2014/2015). Adaptions were made.

2.3 Inclusion criteria

Patients were eligible if they fulfilled the official selection criteria for a basic PMC (age ≥ 18 years, ≥4 prescribed medications for ≥3 months[36]) and if they were taking a VKA (Acenocoumarol, Phenprocoumon) or a DOAC (Apixaban, Dabigatran, Edoxaban, Rivaroxaban) not for orthopedic indication.

2.4 Outcome Variables

Negative or incorrect answers were defined as “knowledge gaps” during the basic PMC (item 2, 3), the semi-structured interview (Items 2-8) and the follow-up interview (items 2-8). Answers to patient’s satisfaction could be given on a 5-point-Likert scale with options ranging from 1 (= ‘I do not agree’) to 5 (= ‘I do agree’). The response category ‘no answer’ was also available. Number of pharmacist-led interventions aiming at increasing knowledge about OAC were retrieved from the standardized protocol the students had filled in.

2.5 Statistical methods

Where appropriate, mean and standard deviations, median and interquartile ranges are presented. Mann-Whitney U test was used to compare numerical data and Chi-Square-test to compare categorical data between groups. McNemar's test was used to compare paired proportions before and after the interviews. Comparison of data before and after interviews was restricted to subjects with full datasets. Data were entered and analyzed using SPSS statistical package version 21.0 (SPSS Inc., Chicago, Illinois, USA) and p-values <0.05 were considered significant.

3. Results

3.1 Participants

A total of 91 students collected data during their internship between November 2015 and June 2016 (n=91 in community pharmacy. Two pharmacies declined participation and eight pharmacies failed to recruit a patient with OAC during the study period.

Out of 81 recruited patients five (6.2%) were lost for follow-up (Table 2). Phenprocoumon was the most common VKA prescribed (Phenprocoumon: 94%, n=47; Acenocoumarol: 6%, n=3). Out of the 31 NOAC patients, 90.3% (n=28), 6.5% (n=2) and 3.2% (n=1) received rivaroxaban, dabigatran and apixaban, respectively. Age, gender, and number of prescribed medication were equally distributed between patients treated with VKAs or with NOACs (Table 2). Duration of treatment with VKA was significantly longer than the duration of treatment with NOAC ($p<0.001$) (Table 2).

3.2 Time

Average time needed to perform an amended PMC and the follow-up interview was 36±15 minutes and 17±12 minutes, respectively, and did not differ between VKA and NOAC patients (data not shown). Average time until follow-up was 15±9 days.

Table 2: Characteristics of patients with VKA or NOAC therapy.

Characteristics	Total	VKA	NOAC	p-value between groups
Number of recruited patients, n (%)	81	50 (61.7%)	31 (38.3%)	
Age in years, mean (SD)	70.7 (12.3)	69.0 (13.1)	73.3 (10.7)	ns
Gender, women (%)	34.6%	28.0%	45.2%	ns
Duration of OAC Therapy, years, mean (SD)	5.8 (5.4)	7.4 (5.7)	3.3 (3.6)	*<0.01*
Number of Rx-Medication, mean (SD)	10.2 (4.3)	9.8 (4.5)	10.7 (4.1)	ns

3.3 Detected knowledge gaps

3.3.1 PMC (A)

Missing data represented 9.9% and 14.8% in item 2 and 3, respectively. The knowledge questions were answered negatively by 6 patients (7.4%; item 2 on “know how”) and 6 patients (7.4%; item 3 “know why”) (Table 3). This lack of knowledge triggered an immediate intervention in 100% and 83.3% of the cases, respectively.

3.3.2 Semi-structured interview (B)

A total of 9 knowledge gaps were detected in item 2 and 3 during the semi-structured interviews, which triggered another immediate intervention in 28.3% and 42.9% of the cases, respectively. Compared to the basic PMC, the semi-structured interview allowed to detect 7 additional knowledge gaps in item 2 and 3.

Items 4 (“underdosage”) and 5 (“overdosage”) were not known in 24.7% (n=20) and 25.9% (n=21) of the cases, respectively (Table 3). The majority of patients (50.6%, n=41) did not know how to proceed in case of a missed dose (item 6; Table 3). Items 7 (“treatment period”) and 8 (“HCP information”) were not known in 11.1% (n=9) and 22.2% (n=18). Identification of knowledge gaps in item 4-8 were followed by an immediate intervention in 28.6-90.0% of the cases.

3.3.3 Follow-up interview (C)

Missing data for the follow-up interview represented 0-1.5%. Percentage of patients with knowledge gaps during the semi-structured interview in items 4,5, 6 and 8 decreased significantly at follow-up (Table 3). Percentage of patients with knowledge gaps in item 7 during the semi-structured interview increased slightly at follow-up. Percentage of patients with at least one knowledge gap during the semi-structured interview decreased significantly from 65.4% to 23.8% at follow-up ($p<0.001$; data not shown).

3.3.4 Differences between VKA and DOAC patients

Patients with NOAC did significantly more often not know how to take their medication (item 2, basic PMC, $p<0.01$) and the effects of overdose (item 5, semi-structured interview, $p<0.05$) compared to VKA patients.

Table 3: Number of knowledge gaps detected during the basic PMC (items 2, 3), the semi-structured interview (items 2-6) and the follow-up interview (items 2-6).

	[A] basic PMC				**[B] semi-structured interview**				**[C] follow-up interview**				before-after comparison	
	Total (n=81)	VKA (n=50)	NOAC (n=31)	p–value*	**Total (n=81)**	VKA (n=50)	NOAC (n=31)	p–value*	**Total (n=81)**	VKA (n=50)	NOAC (n=31)	p–value*	[A-B] (n=81) p-value**	[B-C] (n=76) p-value**
Item 2: "knows how"	**6**	1	5	*<0.05*	**2**	1	1	ns	**1**	1	0	ns	ns	ns
Item 3: "knows why"	**6**	2	4	ns	**7**	3	4	ns	**1**	1	0	ns	*ns*	ns
Item 4: "What happens in case of underdosage"					**20**	11	9	ns	**4**	2	2	ns		*<0.001*
Item 5: "What happens in case of overdosage"					**21**	9	13	*<0.05*	**9**	3	6	*ns*		*<0.001*
Item 6: "What to do in case of a missed dose**"**					**41**	25	16	ns	**13**	11	2	ns		*<0.001*
Item 7: "How long to take the OAC "					**9**	6	3	ns	**10**	5	5	ns		*ns*
Item 8: "Why to inform HCPs about having an OAC therapy**"**					**18**	8	10	ns	**2**	2	0	ns		*<0.005*

*Chi-Square or fishers exact test; **= McNemar's test

3.4 Patient satisfaction

The majority of the patients would recommend the amended PMC to other people (92.0%), was satisfied with the answers by the pharmacists (98.6%) and stated to be more confident how to take the OAC (52.7%) after receiving an amended PMC. The amended PMC did not influence the easiness to take OAC as prescribed (31.6% neutral). More patients agreed that they had less concerns about their OAC after the amended PMC (42.1%) than were neutral (27.6%) or disagreed (30.3%) (Figure 1).

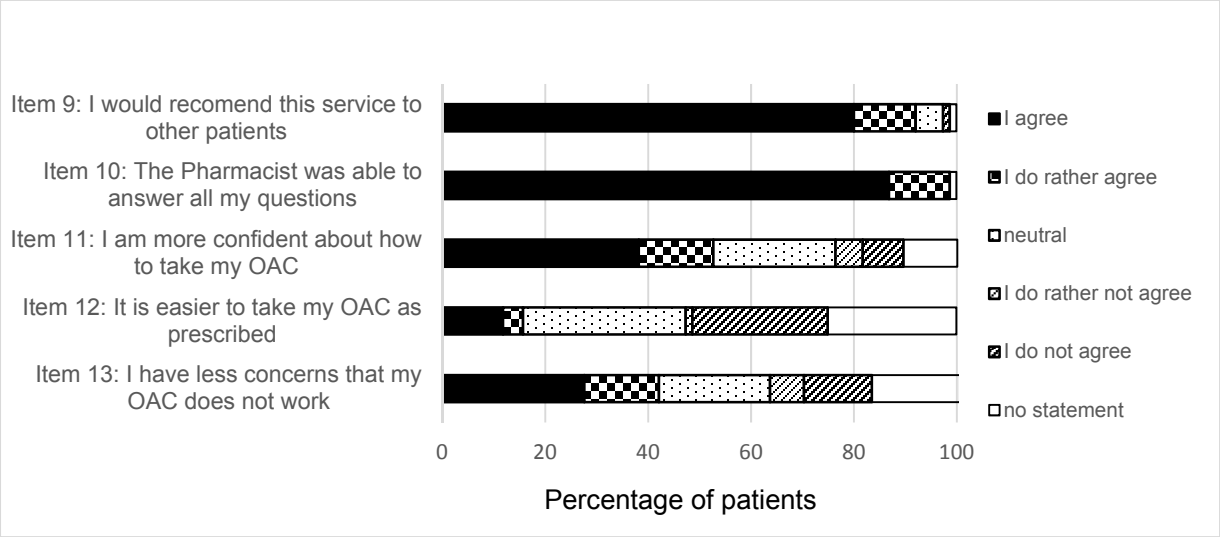


Figure 1: Patients' answers to questions on satisfaction with the amended PMC during the follow-up telephone interview.

4. Discussion

Our findings confirm that a semi-structured interview with specific open-ended questions on medication knowledge enable community pharmacists to detect gaps in patients' comprehension and trigger immediate patient education. Even unstructured but targeted information enhances medication literacy after spontaneous pharmacist-led interventions. Thus, these questions could serve as screening tool.

In our study, 65% of the patients had at least one knowledge gap concerning their therapy with OAC during a semi-structured interview. This is in agreement with other studies that observed that a majority of patients treated with OAC had poor or inadequate knowledge about treatment[152-154]. The specific open-ended question format of the semi-structured interview might be the reason for the detection of additional knowledge gaps compared to the basic PMC, which was developed as a screening tool for any drug related problem linked to polypharmacy. It was shown that open-ended questions enable gathering of qualitative and accurate information [155] and further allow patient-centered communication[63].

Surprisingly, the majority of patients showed knowledge gaps in item 6 ("What to do in case of a missed dose") and around one quarter of patients did not know what happens in case of underdosage or overdosage. A study investigating patient knowledge about warfarin found also that only half of the patients or fewer knew what happens in case of a missed dose, overdosage or underdosage [156]. Beyond that, one study in elderly patients with polypharmacy showed that patients overestimate their knowledge about therapy [157]. These results highlight the necessity to assess patients' medication literacy concerning OAC.

We further found a trend that patients with DOAC therapy were more likely to have knowledge gaps compared to patients on VKAs. Knowledge gaps of patients with DOAC therapy concerned mostly the questions 'How to take the medication?' and 'What happens in case of overdosage?' Compared to patients with VKA therapy, the number of knowledge gaps concerning these two questions was higher. One reason might be the duration of therapy which was significantly shorter in DOAC patients compared to VKA patients, suggesting that contacts of DOAC patients with HCPs and possible education were limited to a few. Another reason may be that routine blood testing in VKA patients allows self-reflection on medication intake behavior and thereby increases awareness of VKA therapy.

It has been shown in observational studies that community pharmacists provide little medication-related information at the counter [71] and about half of the patients do not receive any counseling [72]. Contrary to these findings, we found that detection of poor knowledge through an amended

PMC triggered pharmacists to provide targeted patient education and thereby significantly reduced knowledge gaps. Duration of a counseling session with the amended PMC took a mean of 53±15 minutes, which is about 20 minutes longer than the duration of the basic PMC (29.8±16.5 minutes [36]). Training of pharmacists might reduce the time needed to perform an amended PMC and intervention rate. Furthermore, training for pharmacists incorporating patient-centered type of communication might trigger successful medication intake behavior in patients [158]. However, the duration of the amended PMC might be a barrier for its implementation in practice, if not higher reimbursed as the basic PMC. Additionally, the length of a counselling session may be critical in practice, because advanced age of our population (70.7±12.3 years) which might go along with reduced cognitive capacity leading to loss of concentration. Therefore, it may be reasonable to amend the PMC with specific questions only for high-risk medication, such as OAC. We therefore suggest to further adapt the amended PMC to an “anticoagulation PMC”, similar to the medicines use review in UK, which was also adapted for specific target groups [159]. Within our study, we did not collect data on possible reasons for incorrect answers at follow-up. Assessment of barriers for learning might improve further development of screening questions. Long-term sustainability of the increased knowledge about OAC and subsequent influence on behavior e.g., adherence and save medicines use, need to be addressed in randomized controlled trials.

We acknowledge some limitations. First, the presence of students as observer of a counseling with the amended PMC could have triggered community pharmacists to engage more in counseling practice than usual (also known as the Hawthorne effect [160]). Second, the semi-structured interview consists of eight questions which do not cover all educational domains important for OAC according to Wofford [61]. However, because this study was not VKA specific, topics such as blood-testing and food-drug interactions were omitted on purpose. In further studies, different sets of questions for either DOAC or VKA might be adequate. Third, an increased knowledge might have occurred at follow-up because the study may have increased patients’ awareness of OAC therapy.

4.1 Conclusions

Our study demonstrated that the majority of chronic patients show knowledge gaps concerning their therapy with OAC. Detection of deficient knowledge through the amended PMC triggered pharmacists to provide spontaneous education, which in turn increased patients’ medication literacy. Patients stated to be more confident about how to take their anticoagulant agent after having received counseling through the community pharmacist. Further, patients showed high

acceptance of the service. However, adaptions regarding duration and structure of the counseling and specific screening questions for patients with VKA or NOAC might be helpful before implementing a new pharmacy service in practice.

Conflicts of interest

The authors declare no conflicts of interests.

Other information

The study was developed as an investigator-initiated project by the Pharmaceutical Care Research Group, University of Basel and received partial financial support by Bayer Pharma. The funders had no role in the design, conduct, analyses or writing of this study or in the decision to submit for publication.

Acknowledgements

We would like to thank all participating patients, all involved pharmacists, pharmacy students, all contributors in the study team (namely Sonja Luginbühl and Tamara Imfeld-Isenegger) and Lara Hersberger for data entry.

6.2 Development and validation of a questionnaire to self-assess patient knowledge of direct oral anticoagulants (KODOA–test) [A-2]

Corina Metaxas[1], Valerie Albert[1], Matthias Stahl[2], Kurt E. Hersberger[1], Isabelle Arnet[1]

1 Department of Pharmaceutical Sciences, Pharmaceutical Care Research Group, University of Basel, Pharmazentrum, Klingelbergstrasse 50, 4056 Basel, Switzerland

2 Department of Internal Medicine, Kantonsspital Basel-Land, 4101 Bruderholz, Switzerland

Drug Healthc Patient Saf. 2018 Jul 20;10:69-77.

doi: 10.2147/DHPS.S152954. eCollection 2018. [134]

Abstract

Purpose

Few studies have examined associations between patient knowledge of direct oral anticoagulants (DOAC) and clinical outcomes, mostly because of the lack of validated questionnaires for assessing knowledge. The aim of this study was to develop and validate a questionnaire to self-assess knowledge of DOAC.

Methods

Twelve anticoagulation experts participated in the questionnaire development process to ensure content validity. The Knowledge Of Direct Oral Anticoagulants (KODOA-) test was submitted to patients on DOAC and to pharmacists to assess construct validity. Responsiveness was evaluated after educational counselling. Test-retest reliability was assessed to ensure stability over time and Cronbach's alpha was calculated for internal reliability. Index of difficulty and item discrimination (D-value) were calculated to assess the performance of single items.

Results

The KODOA-test contains 15 items with multiple-choice answers. Each correct answer scores 1 point (max. score of 15). The KODOA-test was administered to 32 patients on DOAC and 28 pharmacists. Pharmacists scored significantly higher than patients at baseline (median score 13.3 vs. 10.0; $p<0.001$), supporting construct validity. Patient scores increased significantly after educational counselling (median score 11 (IQR 2) vs. 14 (IQR 3); $p<0.001$). Test-retest and Cronbach's alpha were acceptable with a Pearson's correlation of 0.8 and an alpha of 0.67. The index of difficulty for most items was satisfactory (0.38-0.72) and the mean D-value was 42.5%.

Conclusions

The KODOA-test is a brief, valid and reliable knowledge self-assessment questionnaire that may be used in clinical trials to investigate associations between knowledge increase and patient related outcomes.

Keywords: Patient knowledge, direct oral anticoagulants, questionnaire development, adherence, validation

Introduction

After a 50 years use of vitamin K antagonists (VKAs) as oral anticoagulant agents (OACs), a new class of substances with different mechanism of action, the direct oral anticoagulants (DOAC) also called non-vitamin K oral anticoagulants (DOAC), has been developed. DOAC are recommended for the prevention and treatment of thromboembolic diseases such as the long-term prevention or treatment of thrombosis [161] and the prophylaxis of stroke and systemic embolism in non-valvular atrial fibrillation (AF) [162]. Controlling of blood values is needed to maintain appropriate anticoagulation with VKAs due to the narrow therapeutic window, which makes the treatment challenging.In contrast to VKA, DOAC do not require routine monitoring, have a fixed dose regimen and no restriction on dietary consumption of vitamin K-containing food. Therefore, DOAC seem more convenient for patients than therapy with VKAs. In practice, use of DOAC to treat AF is increasing [163, 164]. However, due to their short half-life, DOAC's anticoagulant effect is likely to be rapidly reduced after the omission of one dose when no counterbalancing action is undertaken [165]. Thus, DOAC's daily intake requires a strict timing adherence to ensure appropriate therapeutic coverage. Because DOAC do not require consultations for monitoring, the opportunity to discuss aspects of adherence with the patient during such encounters will be missing. Consequently, other ways of insuring adherence to DOAC are required.

Improvement of knowledge and adherence among patients on OACs, in particular DOACs, is needed [154]. For VKAs, enhanced patient knowledge about OACs and the underlying disease was associated with improved long-term adherence or better therapeutic outcomes [81, 82, 166]. To study associations between knowledge and adherence, validated questionnaires are needed to assess patient knowledge about DOACs. To date, various questionnaires exist that assess OAC knowledge. However, only a few have been psychometrically validated, such as the OAK [167], the AKA test [168] and the recently published AKT [169]. Only AKT can be used for VKAs and DOACs. To our knowledge, there is no specific knowledge assessment questionnaire for DOACs available.

The objective of this study was to develop and validate a questionnaire to self-assess patient knowledge about DOACs.

2. Methods

2.1 Trial design

The study was initiated by the Pharmaceutical Care Research Group (PCRG) of the University of Basel. The study was conducted in accordance with the Declaration of Helsinki and has been registered at ClinicalTrials.gov ID NCT03124654. The study was approved by the regional ethic committee (Ethikkommission Nordwest- und Zentralschweiz UBE15/126). All patients gave written informed consent.

2.2 Development of the Knowledge Of Direct Oral Anticoagulants (KODOA)-test

2.2.1 Literature search

A systematic literature search in Medline and Embase was conducted in March 2015 to retrieve published questions assessing patient knowledge about anticoagulation treatment. The search strategy was performed with truncated terms: “Patient* education*” AND “Anticoagulant*” OR “Anticoagulation treatment*” OR “Knowledge” and the limits: English language, human, published from 2005 to march 2015. Abstracts were screened and full texts were retrieved. Two authors (CM, VA) extracted the items of interest. Items regarding VKAs were adapted to DOACs if applicable. Consensus was reached by discussion. Swiss summaries of Product Characteristics (SPCs), the Updated EHRA Practical Guide on the use of non-vitamin K antagonist anticoagulants [113] , the patient guide for taking DOACs from a cardiology patient page [170] and patient information leaflets of the 4 in Switzerland authorized DOACs were used to retrieve additional content. Items were grouped into the 9 educational topics adapted from [61]:

1. Underlying disease
2. Risk-Benefit of treatment
3. Mode of action
4. Application and treatment adherence
5. Accessing health care providers
6. Relevant blood tests
7. Medication interactions
8. Diet and lifestyle
9. Self care

2.2.2 Item reduction and content validity

A panel of experts was created with 12 helath care proffesionals (HCP; 4 nurses, 4 pharmacists, 4 physicians) who had experience with DOAC patients.They selected the relevant items for patient knowledge of DOAC and determined the extent to which the items represent the construct of interest (content validity) [171].

The item reduction occurred with an online survey (2 rounds) followed by a focus group discussion. The 9 educational topics (first round) and the single items (second round) were ranked in descending order (1st =most relevant, last =most irrelevant topic). The focus group discussion aimed at defining which items had to be included in the questionnaire by defining a threshold above which the items were perceived as relevant for patient knowledge. Discussion and setting threshold occurred by voting until a consensus was found (unanimity). The session was recorded and transcribed verbatim.

2.2.3 Answer format

Answers to the items were developed as multiple-choice format because this is the most appropriate and efficient form for assessing cognitive knowledge [79]. One correct and two incorrect response alternatives were adapted from the original article when available or newly created. Score was defined as 1 for a correct response and 0 for an incorrect or no response. Confidence about the given response was assessed with a single question with a yes/no answer option.

2.2.4 Educational manual with correct answers as counseling guide

A manual with referenced correct answers and background information about the reason for correctness was generated in order to standardize the education provided to patient. The manual is not supposed to be given to patients. The manual starts with an instruction section about how to dispense the educational counseling. The HCP is invited to discuss systematically each question with the patient. Whenever the patient gave a wrong answer or ticked to be uncertain about the question, HCPs are instructed to give the correct answer with background information according to the manual. Then HCPs should ask if the issue is clear or if patient needs further information. When every question of the KODOA-test has been discussed as described, HCPs should ask patient if there are any unanswered questions about their DOAC. Although not part of the questionnaire, information about intake time of DOAC was added to cover all instructions needed to counsel. The manual was used by two investigators (CM and VA) during counseling sessions.

2.2.5 Pilot testing

Comprehension and readability of the finalized KODOA-test was presented to the experts who participated in the focus group discussion, and five patients who were not included in the validation study. They rated structure, content, comprehension and response alternatives by writing commentaries in free text. Adaptions were made accordingly.

2.3 Validation of the KODOA-test

2.3.1 Patient eligibility

Patients were eligible if they filled a prescription for DOAC (rivaroxaban, edoxaban, dabigatran, or apixaban) in a community pharmacy or if a DOAC was present in their medical record, if they suffered from atrial fibrillation, deep vein thrombosis, or pulmonary embolism, if they were ≥18 years old and if they were able to give written informed consent in German. Patients with an orthopedic indication for DOACs, with dementia, or lack of written and/or oral understanding in German were excluded from the study.

2.3.2 Data collection

A selection of community pharmacists engaged as experts for the state exams of the University of Basel were invited to participate in the research and asked to distribute this invitation to all community pharmacists with whom they were working. Three dedicated community pharmacies located in Basel and Münchenstein accepted to serve as recruiting places. Pharmacy staff asked patients with a prescription for DOACs to participate in the study and handed out the patient information and the informed consent forms. Patients who agreed to participate fixed two appointments within two weeks at the community pharmacy.

Patients filled in the KODOA-test four times. During the first appointment at the community pharmacy (T1), feasibility and acceptability were also assessed. Immediately after patients filled in the KODOA-test, they rated on a 4-point Likert scale structure, readability and time to fill in the questionnaire, comprehensibility and ambiguity of the items and the available answer options.

During the second appointment at the community pharmacy patients (T2), patients received educational counseling according to the wrong given answers. Immediately after, patients filled the KODOA-test a further time (T2+edu). Test-retest was assessed with answers from T1 and T2; responsiveness with answers from T2 and T2+edu.

Approximately two weeks after T2, patients received the KODOA-test by post mailing (with a paid reply envelope) and filled it at home (T3) to assess sustainability of the educational counseling. Patient follow-up by the treating physician (general practitioner or cardiologist) took place as usual.

Patient characteristics were obtained through written survey at T1 and included demographic (age, gender, educational background, duration of DOAC therapy) and three health literacy questions: Difficulties to understand written information about medication (yes/neutral/no); Difficulties to understand verbal information about medication (yes/neutral/no); Confidence when filling out forms (yes/neutral/no). One question assessed self-estimated knowledge of DOAC with the answer options: bad, moderate, good or excellent. At T3, patients were asked to rate following statement on a five point Likert Scale: “After educational counseling I know more about my DOAC” (1=I do agree; 5=I do not agree).

A personal letter was sent to 29 pharmacists asking them to answer the KODOA-test without consulting additional media and to return it using a pre-paid reply envelope.

2.4 Statistical methods

Where appropriate, frequencies, mean and standard deviations or median and interquartile ranges are presented. Kruskal-Wallis test was used to compare numerical variables between four groups. All data were entered and analyzed using SPSS statistical package version 24.0 (SPSS Inc, Chicago, Illinois, USA) and p-values <0.05 were considered significant.

2.4.1 Validation parameters

Construct validity was tested with the method of contrasted groups [172]. Construct validity would be confirmed if the median test score of pharmacists was significantly higher than median test score of patients at T1. Mann-Whitney U Test was used to compare numerical data between groups. At T2 patients received educational counselling about DOACs and responsivness of the KODOA-test was tested. Median test scores before (T2) and after educational counselling (T2+edu) about DOACs were compared using Wilcoxon test.

The test–retest method was used to demonstrate the stability of the questionnaire over time. Pearson’s correlation coefficient was calculated between the test scores from T1 to T2 and T2+edu to T3. Additionally, internal consistency or reliability was assessed using Cronbach’s alpha, which indicates whether each item of a scale is appropriate for assessing the underlying concept of its scale. Values for Cronbach’s alpha range between 0 and 1; the closer they are to

0, the less the items are related to one another. Values between 0.5-0.7 are the minimal requirement to indicate satisfactory internal consistency [173].

Index of difficulty and item discrimination (D-value) were calculated to assess performance of single items. The index of difficulty is defined as the proportion of patients answering the item correctly (=number of correct responses/total number of responses). An item with an index of difficulty >0.75 is deemed to be too frequently answered correctly [174]. Item discrimination (D-value) tests how well an item discriminates between people who have a low and high knowledge score. A D-value is calculated by subtracting for each item the proportion of respondents answering correctly in the lowest quartile from those answering correctly in the highest quartile, aiming for a mean D-value of 50% [174].

3 Results

Out of 45 compiled items, the expert panel selected 15 to be important for knowledge about DOACs. The 15 items were derived from the educational topics “Application and treatment adherence” (5 items, nb. 3, 5-8), “Risk-benefit of treatment” (2 items, nb. 2, 4), “Accessing health care providers” (2 items, nb. 12, 13), “Self-care” (2 items, nb. 9, 15), “Relevant blood tests” (1 item nb. 14), “Medication interactions” (2 items, nb. 10, 11), and “Mode of action” (1 item, nb. 1). Two versions of the KODOA-test were developed, one for patients with atrial fibrillation and one for patients with deep vein thrombosis or pulmonary embolism. The two versions differed in the answer options in items 2, 3 and 4, depending on the underlying disease (Appendix).

Out of 67 invited patients, 32 participated (Table 1). They were prescribed either rivaroxaban (84.4%) or apixaban (15.6%). Mean duration of DOAC use was 1.8 ± 1.7 years. Patients had mandatory education (n=3), technical/vocational education (n=11), a higher school certificate (n=11), University degree (n=4) or did not give any information (n=3). A majority of patients stated to have no difficulties to understand written and verbal information about medication and to be confident when filling out forms (Table 1). One patient (3.1%) was lost for follow-up (T3) and one patient did not fill in the knowledge question for follow-up evaluation.

Table 1: Patient and pharmacists characteristics at T1 (baseline)

	Patients (n=32)				Pharmacists (n=28)
Female (%)	65.5				89.0
Age (years; mean ± SD)	73 ± 9				34 ± 9
Indication (%) Atrial fibrillation Deep vein thrombosis/pulmonary embolism	 62.5 37.5				
Duration of therapy (years, mean ± SD)	1.8 ± 1.7				
Comprehension of written information about medication (%) Without difficulties Neutral With difficulties	 46.8 21.9 31.3				
Comprehension of verbal information about medication (%) Without difficulties Neutral With difficulties	 75.0 12.5 12.5				
Confidence when filling out forms (%) Confidence No confidence	 93.8 6.2				
Self-estimated knowledge (% of patients, [number of patients])	Bad 9.4 (n=2)	Moderate 31.3 (n=10)	Good 53.0 (n=17)	Excellent 6.3 (n=2)	
KODOA-test scores (mean ± SD)	11.0±4.4	8.2 ± 2.4	10.9 ± 2.1	10.5 ± 3.5	
Number of ticks “being certain about the correctness of the given answer” (mean ± SD)	7.7 ±1.5	9.6 ± 3.4	10.9 ± 2.6	12.5 ± 2.1	

Feasibility was confirmed. Mean time to fill in the KODOA-test was 7.8 ± 3.0 minutes and patients were satisfied with the structure, readability, comprehension and time to fill in the questionnaire (Figure).

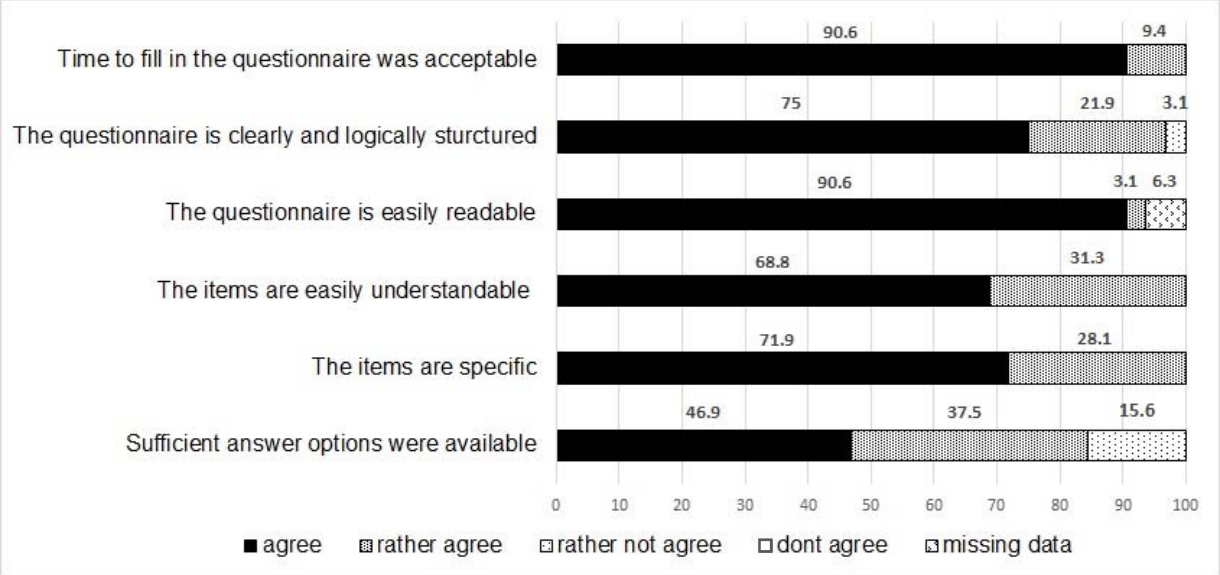


Figure: Patients' answers to questions regarding feasibility of the questionnaire (n=32).

Twenty-eight pharmacists (34 ± 9 years, 89% women, 8 ± 9 years working experience) filled in the KODOA-test. Median test score of community pharmacists (13.0 (IQR 1)) was significantly higher compared to test score of patients (10 (IQR 4)) at T1 (U-Test: $p<0.001$). Median test score of patients at T2 was 11 (IQR 2) and increased significantly to 14 (IQR 3) after educational counseling (Wilcoxon: $p<0.001$). Educational counseling about DOAC lasted 14 ± 7 minutes. The median number of items whose answers were correct and ticked as confident was calculated. This number increased from 9 (IQR 3) at T2 to 14 (IQR 1) after educational counseling at T2+edu (Wilcoxon: $p<0.001$).

Reliability of the KODOA-test was demonstrated. Test-retest reliability between T1 and T2 (r=0.800, p<0.001; 12 day mean duration between the tests) and between T2+edu and T3 was confirmed (r=0.644, p<0.001; 17 days mean duration between the tests) (Table 2). Internal consistency was acceptable (Cronbach's alpha=0.67). Cronbach's alpha increases slightly (0.673 to 0.678) if items 3, 5, 6 or 11 are excluded (Table 3). The index of difficulty for most items was satisfactory (0.38-0.72) (Table 3). The mean D-value was 42.5%.

Table 2: Mean test scores, i.e. correctly answered questions (± SD) at T1, T2, T2+edu (after educational counselling) and T3.

Visit	Patients (n=32)	Pharmacists (n=28)	p-value
T1	10.03 ± 2.7	13.3 ± 1.0	<0.001
T2[a]	10.06 ± 2.1	NA	
	**		
T2+edu	13.9 ± 1.2		
T3[b]	13.1 ± 1.7	NA	

NA= not applicable

[a] mean duration between tests: 12 days

[b] N=31 for retest score ; mean duration between tests: 17 days

**p<0.001

There was no relationship between KODOA-test scores at T1 and patient self-estimated knowledge of DOAC (Table 1). Patients with higher self-estimated knowledge tended to answer with more confidence (Table 1). At T3, all patients agreed that they knew more about their DOAC after having received educational counseling.

Table 3 Content and psychometric properties of the KODOA-test items

Item nr.	content	Patients with correct answer (%)	Index of difficulty	Item discrimination	Cronbach's α if item is omitted
1	Name of the DOAC	93.8	0.94	18.2	0.660
2	Duration of therapy	90.6	0.91	18.2	0.669
3	Dosing frequency	81.3	0.81	45.5	0.673
4	Indication for DOAC	93.8	0.94	18.2	0.656
5	What to do if uncertain whether last dose was ingested	43.8	0.44	47.7	0.673
6	What to do in case of a missed dose	37.5	0.38	35.2	0.678
7	What to do in case of double dosing	37.5	0.38	56.8	0.645
8	Does the DOAC work when vomiting immediately after ingestion	37.5	0.38	81.8	0.640
9	Most frequent side effect	59.4	0.59	47.7	0.647
10	Safest OTC analgesic with DOAC	53.1	0.53	47.7	0.640
11	Whom to ask about safe OTC	90.6	0.91	5.7	0.673
12	When to inform others about DOAC therapy	87.5	0.88	27.3	0.655
13	Recognition of emergencies	65.6	0.66	81.8	0.605
14	How often to visit the doctor for lab monitoring	59.4	0.59	51.1	0.652
15	Carrying an anticoagulation card	71.9	0.72	54.5	0.638

OTC= Over the counter

Discussion

The KODOA-test was confirmed to be feasible, comprehensive, reliable and valid to self-assess patient knowledge of DOAC. Furthermore, the KODOA-test is responsive to change. Content validity was ensured by a developing process with experts of different professions taking care of patients undergoing anticoagulation therapy in their daily practice. Construct validity was supported by significant differences in scores between patients and pharmacists. Finally, the KODOA-test was responsive to educational counseling on DOAC, supporting construct validity.

Patients were able to complete the test within 8 minutes and rated this time as acceptable. Compared to other assessment questionnaires for knowledge about oral anticoagulation therapy the KODOA-test is relatively brief. The AKT and AKA assessment questionnaires need 10-15 minutes and 20 minutes to be filled in, respectively [168, 169].

The index of difficulty of most items and mean D-value was satisfactory. Although six items showed a poor level of difficulty, they were retained because they are related to core information about DOAC therapy, such as name, treatment duration or whom to ask in case of pharmaceutical questions. The KODOA-test showed moderate internal consistency, with a Cronbach's alpha of 0.67. The obtained Cronbach's alpha value is likely a result of the multifactorial nature of the KODOA-test, because it consists of items derived from several educational topics. Omission of single items had minimal effect on Cronbach's alpha. The KODOA-test included very easy items and very difficult items. Despite the fact that such grade of difficulty tends to decrease the internal consistency of the scale [175], HCPs need basic questions on the medication used by the patient such as dosing frequency. Finally, a low Cronbach's alpha might be explained by the shortness of KODOA-test with 15 questions, since internal consistency increases as test length increases [176]. Therefore, an alpha of 0.67 seems acceptable.

Stability over time was confirmed by test-retest correlation above the threshold of 0.7, which indicates adequate reliability [177]. The mean time between test and re-test was 12 days. Recommendations for interval between two identical tests vary between two days [175] and three months [178]. Two studies investigating knowledge about anticoagulation with questionnaires had longer interval of two to three months for test re-test [167, 169] and two further studies on knowledge about nutrition had intervals of two weeks [179, 180]. We selected a short time interval based on ethical considerations, because patients with deficient knowledge should be corrected as soon as possible in order to avoid life threatening situations. Knowledge scores remained high after approximately two more weeks demonstrating the sustainability of the educational counselling. In addition, patients agreed uniformly that their knowledge had increased.

Nevertheless, further follow-ups could be useful to maintain a high level of knowledge. State of the art currently in Switzerland and in many other countries is silo interventions from several HCPs. It would be best practice to share information and questionnaire results between HCPs.

The majority of patients rated their knowledge about DOACs at baseline as good or excellent. However, this self-estimation did not correspond to KODOA-test scores suggesting that patients both overestimate and underestimate their knowledge. Consequently, self-estimation of knowledge with a single question should be taken with caution. Further, asking confidence when answering the item is subject to the same under- and overestimation. However, because of the low number of patients in the bad and excellent self-estimated knowledge groups, this finding needs further investigation.

Interestingly, patients' scores after educational counselling were still below the maximum with an average of 1.9 erroneous answers. The items concerning safety issues (missed dose, double dosing, vomiting) seemed difficult to remember. HCPs should be aware that some pharmacological concepts are more demanding than others.
Previous studies observed an increase of knowledge about oral anticoagulation therapy following education [181-184]. However, only one study included patients with DOACs, but knowledge assessment methods were not developed for patients on DOAC therapy [181]. In a recent study, the development of an oral anticoagulation knowledge questionnaire was reported [169]. The AKT contains 20 items applicable for DOAC patients and 8 additional items for VKA patients. Overall, the AKT seems to be a valid and reliable questionnaire to measure patient knowledge about oral anticoagulants. However, it is not reported whether the AKT is responsive to change and scoring seems more complicated as with the KODOA-test. In light of these inconveniences, KODOA-test is likely to be easier to use in patient studies.

Our study has several strengths. First, we followed an evidence-based approach to select items. We coupled a literature search to educational theory to reduce the number of items to the minimum needed to assess knowledge. Second, we used the most recent publication such as the EHRA guidelines to cover exhaustively the characteristics of anticoagulation therapy. Third, we selected experts in all fields of the health care professions to determine the relevant items needed in a self-assessment questionnaire. Fourthly, we tested pharmacists as representatives of health care professionals. We are confident that similar knowledge results would have been obtained with doctors and nurses. Finally, we developed a manual with answers to obtain standardization of

educational counseling. By doing so, we offer a fast and efficient way of counseling to all healthcare professionals who provide information for patients.

We acknowledge some limitations. First, 52.3% of the patients refused to participate in the study. Time consumption (i.e. two visits at the community pharmacy) was likely the reason of this moderate acceptance rate, rather than a low acceptability to answer the KODOA-test. Secondly, the relatively small number of subjects may limit the ability to generalize results to all patients on DOAC. Importantly, sample size was adequate to show that the KODOA-test is responsive to change and that construct validity is given (data not shown). Thirdly, this study included elderly Swiss German speaking patients with an indication of AF or DVT/PE and taking rivaroxaban or apixaban that is, only two of the four commercially available DOACs in Switzerland. Because the KODOA-test targets DOAC knowledge in general that is, independently of the anticoagulant agent, we cannot think that patients on other anticoagulants (i.e. edoxaban or dabigatran) or in another setting (i.e. after surgery) would have answered differently. Applicability of the KODOA-test in other settings should nevertheless be investigated in a further study. Finally, the multiple-choice format permits guessing, which may have increased scores in patient and pharmacist group.

Conclusions

The KODOA-test showed to be valid and reliable in Swiss German speaking elderly outpatients taking DOAC. The application of the KODOA-test in other populations needs confirmation by further research. To our knowledge, the KODOA-test is the first validated questionnaire specific for patients taking DOAC that is responsive to educational counseling. Therefore, the KODOA-test could be used in clinical trials where associations between knowledge of DOAC and adherence or clinical outcomes are of interest.

Conflicts of interest

The authors declare no conflicts of interests.

Other information

The study was developed as an investigator-initiated project by the Pharmaceutical Care Research Group, University of Basel and received partial financial support by Bayer AG. The funders had no role in the design, conduct, analyses or writing of this study or in the decision to submit for publication.

Acknowledgements

We would like to thank all experts participating in the development process of the KODOA-test, the three community pharmacies for patient recruitment and all patients and pharmacists for participating in the validation study. We thank Susanne Habegger for her contributions to the literature review and Sonja Luginbühl for the organization of the focus group discussion and KODOA-test piloting. We thank William Caddy for proofreading.

7 Project B: Patient preferences and vitamin B12 deficiency

7.1 Impact of type 2 diabetes and metformin use on Vitamin B12 associated biomarkers - an observational study [B-1]

Metaxas Corina[1], Zurwerra Chantal[1], Rudofsky Gottfried[2], Hersberger Kurt E[1], Walter Philipp N[1,3]

1 Pharmaceutical Care Research Group, University of Basel, Switzerland
2 Department of Medicine, Kantonsspital Olten, Switzerland
3 Institute of Laboratory Medicine, Solothurn Hospitals, Switzerland

Exp Clin Endocrinol Diabetes. 2018 Jun;126(6):394-400.

doi: 10.1055/s-0043-120760. Epub 2018 Feb 2. [135]

Abstract

Aims

Assessment of the impact of type 2 diabetes (T2DM) and metformin use on vitamin B12 (VB12) associated biomarkers and their suitability to represent VB12 supply.

Methods

Differences of VB12, holotranscobalamine (HoloTc), the biologically active fraction %AB12=HoloTc/VB12*100 and homocystein (Hcy) were analysed i) among diabetic outpatients with (DMMet+) and without metformin use (DMMet-) and ii) in comparison to an external non-diabetic reference group with low VB12 (<200pmol/L).

Results

VB12 associated biomarkers were distributed equally between T2DMMet+ (n=29, 58%) and T2DMMet- (n=21, 42%). Significant differences in %AB12 in diabetic patients with low VB12 (n=19) compared to the non-diabetic reference group (n=31) were found. Higher %AB12 was associated with diabetes. Hcy levels were significantly associated with age, folic acid level, renal function and HoloTc but not with VB12.

Conclusions

In T2DM patients with low VB12, %AB12 was confirmed as being higher in comparison to nondiabetic patients. The effect was not clearly attributable to metformin use. HoloTc was unaffected by the lowering of VB12 and significantly associated with the functional marker Hcy. Both findings support the use of HoloTc for the assessment of VB12 supply in diabetic patients.

Keywords: T2DM, metformin, vitamin B12 deficiency, vitamin B12, holotranscobalamine

Introduction

Recently, an increased frequency of VB12 deficiency among T2DM patients has been documented by several cross sectional studies and case reports [185]. Clinically, VB12 deficiency in adults may result in nonspecific symptoms such as tiredness, loss of appetite, hematologic manifestations (megaloblastic anemia), neurologic symptoms (e.g. polyneuropathy, ataxia), as well as symptoms of a psychiatric nature (e.g. depression) [119, 130]. Additionally, cardiovascular manifestations associated with hyperhomocysteinemia were mentioned [186-189].

Clinical symptoms of VB12 deficiency in T2DM are comparable to those in the general population. Worsening of diabetic neuropathy has been described among patients with co-existing vitamin B12 deficiency. Furthermore, VB12 replacement has been shown to cause symptomatic improvement, reduction in pain, and paranesthesia among patients with severe diabetic neuropathy [185] , suggesting that functional VB12 deficiency in T2DM patients is clinically significant. Sensory polyneuropathy caused by VB12 deficiency mimics diabetic neuropathy [190]. Overlapping symptoms between T2DM and VB12 deficiency may complicate its clinical suspicion (or diagnosis). Biochemically, VB12 deficiency is characterized by subnormal to borderline VB12 values in serum (<148-221 pmol/l) [122]. Holotranscobalamine (HoloTc) is the bioactive form of VB12 and makes up to 20% of the total vitamin B12 concentration in the human body [123]. It has been discussed as a more specific and sensitive marker of VB12 deficiency [124-126]. Broad ranges of cut-off points for HoloTc have been described as <20 – 50pmol/l [127]. Functional VB12 deficiency is characterized by elevated homocysteine (Hcy) and/or methylmalonic acid (MMA) levels [122].

Additionally, the clinical biochemistry of VB12 is influenced by diabetes and its treatment. Systematic observations in clinical trials as well as biochemical studies in animals raised questions on possible interactions between diabetes, metformin treatment, and VB12 metabolism. It has been proposed that the increased oxidative stress in diabetes is involved in the pathogenesis of functional VB12 deficiency [128]. Treatment of T2DM patients with metformin has been reported with reductions of 10-20% in plasma VB12 levels [191-195]. Metformin may impair VB12 absorption and thereby induce VB12 deficiency [195, 196]. One study described the correlation of cumulative metformin dose, low VB12 levels and clinically more severe peripheral neuropathy [190]. Given the widespread use of metformin as first line treatment for patients with diabetes and normal kidney function, its effect on VB12 metabolism is remarkable [197]. Metformin is a biguanide. It’s mechanism of action primarily involves decreasing hepatic glucose production and increasing glucose uptake [198]. Because VB12 deficiency is a reversible cause of demyelinating nervous system disease and bone marrow failure, its early detection and treatment are important [130].

Therefore, the identification of metformin as a risk factor for the development of VB12 deficiency is important and the evaluation of VB12 status is recommended [199]. However, there is reasonable doubt whether the reductions of VB12 levels reflects a true decrease in VB12 supply. A recent study in patients with diabetes (> 65 years old) which were treated for 3 months with metformin showed that the inactive part of VB12 bound to haptocorrin is reduced in metformin-treated patients but not in the control group (non significantly) [200]. Additionally, a study in rats found that metformin treatment increases liver accumulation of VB12 thereby resulting in decreased circulating VB12 and kidney accumulated VB12 [201]. The same authors found a significant reduction of serum VB12 but not HoloTc after 6 months of metformin treatment in women with polycystic ovarian syndrome (PCOS) [129]. These findings raise the question of whether low serum VB12 observed in patients treated with metformin actually reflects VB12 deficiency and rather supports the hypothesis of altered metabolism of VB12 in metformin-treated patients.

In this study, the effect of metformin treatment on VB12 status as reflected by total VB12 and HoloTc in T2DM patients is investigated. In particular, the %AB12 in T2DM patients with and without metformin treatment was compared and interactions between VB12, HoloTc and homocystein were analysed. Additionally, the impact of diabetes itself on VB12 associated biomarkers at low VB12 levels is investigated in a subgroup of patients with diabetes in comparison to an external reference group of non-diabetic patients

Materials and methods

This was an observational cross-sectional trial approved by the ethics committee of northwestern Switzerland (EKNZ), and was registered at ClinicalTrials.gov NCT02111967. The study was conducted in accordance with the Declaration of Helsinki and correspondent to International Conference on Harmonization Good Clinical Practice (ICH-GCP) guidelines. All patients gave written informed consent. Patients for the external reference group were included from a previous study (ClinicalTrials.gov NCT01832129). The primary hypothesis was that VB12 would be lower in T2DM patients treated with metformin while HoloTc levels would not differ compared to T2DM patients without metformin treatment.

Setting

The study included adults with type 2 diabetes and an external reference group of nondiabetic and metformin-naïve patients. Patients with T2DM were classified as metformin users (DMMet+) if they were treated with metformin for at least 6 months or as metformin-naïve patients (DMMet-), when no prior use of metformin was reported (Figure 1; A). Participants with newly initiated metformin (< 6 months usage), concurrent intake of preparations containing VB12 (in the last 3 months), diagnosis of transcobolamin transporter defect, diagnosis of vitamin B6 deficiency, diagnosis of liver disease with CHILD-PUGH scores B and C, acute hepatitis and diagnosis of alcohol abuses (defined as a diagnosed condition or by self-reported daily intake of alcohol), diagnosis of renal insufficiency stadium III, IV and V (KDOQI), acute renal diseases or renal function below 60ml/min according to the Cockroft Gault' equation were excluded from the study. For the reference group data from patients from a previous study were used [136]. Out of 37 patients 4 were excluded due to an alcohol use disorder (n=4).(Figure 1).

Patient Recruiting

Patients with diabetes with (DMMet+) and without metformin treatment (DMMet-) were recruited during a routine visit at their diabetes specialist (Figure 1; sample A). Patients with diabetes and serum VB12 levels below 200pmol/L were classified as VB12 deficient (LVB12-DM). The external reference group of non-diabetic patients with low VB12 levels (LVB12-Ref) was established from a previously published study that recruited outpatients during a routine visit to their general practitioner. If patients had a diagnosis of diabetes, they were not excluded but assigned to the LVB12-DM Group (Figure1, sample B).

Questionnaires and physical examinations

Patients were asked to fill in a questionnaire about their nutrition, co-medication and demographics. Patients with type 2 diabetes were screened for neuropathy signs using the Neuropathy Symptom Score (NSS) and the Neuropathy Disability Score (NDS) [202].

Pharmacological biomarker

All venous blood samples were analyzed for VB12 (Beckman Coulter® DxC 860i), HoloTc (Abbott Architect® i2000SR) and Hcy (Roche Cobas® 6000). The biologically active fraction %AB12 was calculated by dividing HoloTc/VB12*100. Blood cell count was determined on a Beckman Coulter DxH 800. Cut-off values defining VB12 deficiency were VB12: <200pmol/L, HoloTc: <37pmol/L and Hcy :> 15μmol/L. Blood samples of patients with VB12 levels below <200pmol/L were re-analyzed for VB12 on the Roche ® 6000 to directly compare the results with the external reference group.

Study size

Based on published data, patients with diabetes were assumed to display VB12 levels of approximately 400 pmol/l, with an estimated standard deviation of 250 pmol/l (62.5%) [203]. In this study, 40.1% of patients had consumed VB12 supplements; therefore, we concluded that the standard deviation among patients without VB12 supplements was approximately half of the observed standard deviation (30%). A reduction in plasma VB12 levels of 20%-24% is described in the scientific literature [200]. Since we expected a reduction in levels, a one-tailed test was applicable. Based on a reduction of VB12 levels of 24%, a total of 50 samples had had to be analysed to ensure that the 80% confidence interval includes the true difference of means with a α-significance level of 5%.

Statistical analysis

Values are given as medians with quartiles and percentages where appropriate. Frequencies were analyzed using Chi-square tests or Fishers test. The Mann-Whitney test was used to compare numerical variables between two groups. Bivariate correlation was performed when association between two scaled variables was assessed. A p-value ≤0.05 was considered significant. Multiple linear regression analyses were conducted to calculate i) the relative impact of VB12 and HoloTc on Hcy in relation to age, renal function assessed as estimated Glomerular filtration rate (eGFR) according to the Cockroft-Gault' equation, and folic acid levels and ii) the relative impact of diabetes, age, BMI, renal function and folic acid levels on VB12/HoloTc ratio using a stepwise

method to include the independent variables. The statistical procedures were performed with SPSS statistical software Version 24 (SPSS Inc., Chicago, Il, USA).

Results

Participants

Between March 2014 and August 2014, 50 outpatients with diabetes were recruited within the endocrinology unit. Recruitment and patient characteristics of the external reference group have been described elsewhere [136]. Two of the 37 recruited subjects in this study had diabetes and were thus integrated in the respective subgroup for the analysis of VB12 associated biomarkers in diabetes (Figure 1). Patient characteristics of T2DM patients (29 DMMet+; 21 DMMet-) were equally distributed (Table 1).

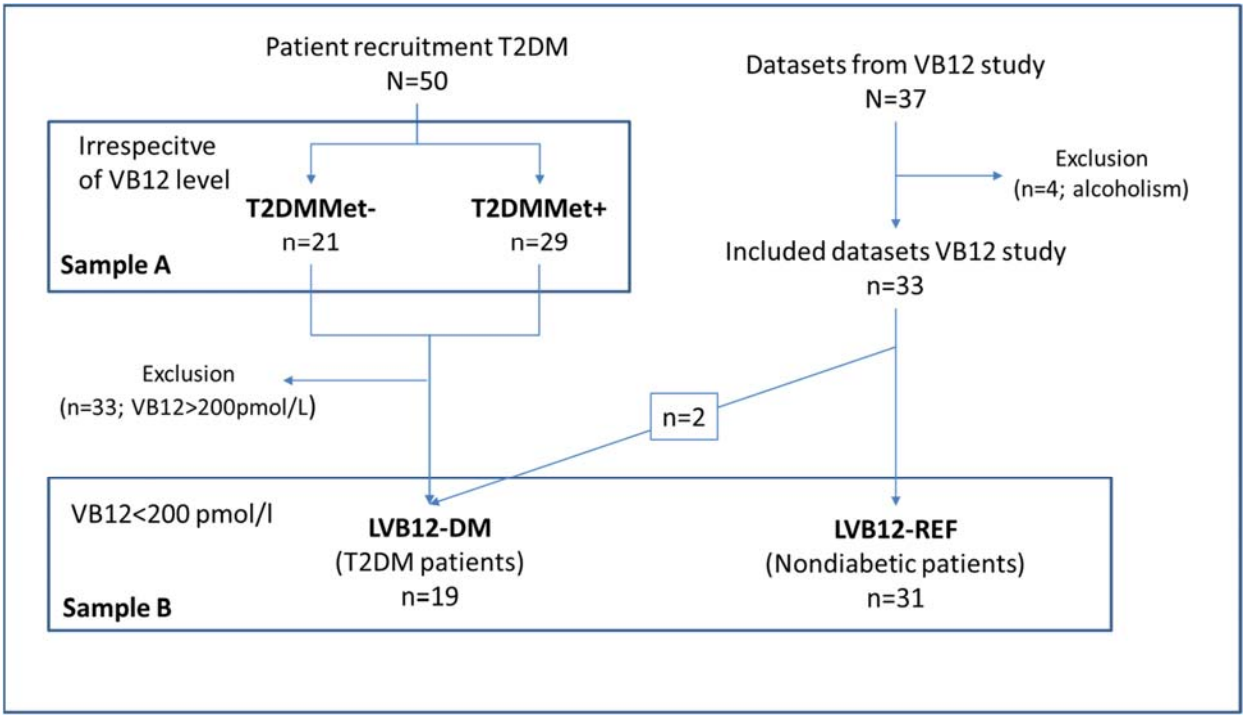


Figure 1. Sample A) Patients recruited by the diabetologist. Comparison of VB12, HoloTc and VB12/HoloTc-ratio between DMMet+ and DMMet- and assessment of associations between VB12, HoloTc, Hcy and severity of neuropathy. Sample B) Patients with low VB12 (<200pmol/L) recruited by diabetologist and general practitioners. Comparison of VB12, HoloTc and VB12/HoloTc-ratio between LVB12-DM and LVB12-Ref.

Table 1: Patient characteristics of sample A and potential risk factors for the development of VB12 deficiency of DMMet+ group and DMMet- group. Parameters are given as median and 25/75 percentiles if not otherwise indicated.

	DMMet+ (n=29)	DMMet- (n=21)	p-value
Age (years)	60 (53/70)	64 (55/72)	0.42
Women (%)	44.8	38.1	0.43
BMI (kg/m2)	30.9 (24.9/40.6)	33.8 (30.2/37.8)	0.33
Years with diabetes	7 (4/15)	12.5 (5.5/20)	0.10
HbA1C (%)	7.7 (6.7/8.4)	8.7 (6.9/9.8)	0.17
NSS+NDS	6.5 (2.8/11.3)	11 (5.3/14.8)	0.09
eGFR (Cockroft Gault)	115 (78.4/160.4)	116 (74.7/157)	0.78
Proton-pump inhibitors use (%)	6.9	19.0	0.22
Antacid and H_2 Blocker use (%)	0	0	-
Vegetarians (%)	6.9	0.0	0.33
Vegans (%)	0.0	0.0	-

VB12 associated biomarker levels in diabetes patients (sample A)

DMMet+ versus DMMet-

Vitamin B_{12} serum levels and HoloTc levels were slightly lower in DMMet+ patients compared to DMMet-, but not significantly (VB12: -10.4%; HoloTc: -9.2% Table. 2). The %AB12, Hcy and blood count levels were equally distributed between the two groups (Table 2). Out of 50 patients, 17 (34%) had a VB12 value below 200pmol/L (11 DMMet+ (39.3%) and 6 DMMet- (28.6%); Fishers-test: 0.55), 3 (6%) had a HoloTc value below 37pmol/L (3 DMMet+ (10.3%) and 0 DMMet- (0%); Fishers-test: 0.25) and 16 (32%) had a Hcy level above 15µmol/L (10 DMMet+ (34.5%) and 6 DMMet- (28.6%); Fishers-test: 0.75) (data not shown).

Table 2: VB12 associated biomarker and blood count levels of DMMet+ and DMMet- groups. Parameters were given as median and 25/75 percentiles, respectively.

	DMMet+ (n=29)	DMMet- (n=21)	p-value
VB12 (pmol/L), Beckman	224 (163/263)	250 (190/344)	0.19
HoloTc (pmol/L)	79.9 (46/102)	88 (68/111)	0.09
%AB12	30.1 (25.0/40.8)	35.4 (29.5/39.6)	0.32
Hcy (µmol/L)	12.9 (11.3/17.5)	11.8 (10.5/19.3)	0.55
Hb (g/L)	142 (133/154)	145 (139/152)	0.71
MCV (fL)	90 (88/93)	93 (88/96)	0.12
MCH (pg)	30 (29/31)	31 (30/32)	0.07

Correlations of VB12 associated biomarkers

Significant correlations ($p<0.05$) of VB12 levels with age ($r=-0.42$) and Hcy ($r=-0.37$) were found for the entire study population, as well as with metformin dose (-0.43) and renal function ($r=-0.41$) in DMMet+ patients. For HoloTc significant correlations were limited to Hcy ($r=-0.44$) and Metformin dose ($r=-0.47$) in DMMet+ patients. High Hcy levels were associated with high age ($r=0.35$), low renal function ($r=-0.48$) and low folic acid levels ($r=-0.36$) in the entire study population. Mean daily metformin dose in DMMet+ group was 1.9g ±0.6g (range: 1.0g - 3.0g).

Prediction of Hcy levels

In a multiple linear regression model, a significant association of Hcy with age ($\beta=0.325$; $p=0.029$), folic acid ($\beta=-0.359$; $p=0.003$), HoloTc levels ($\beta=-0.300$; $p=0.01$), and renal function expressed as eGFR by Cockroft-Gault ($\beta=-0.343$; $p=0.014$) was found in all DM patients ($r^2=0.539$; $p=0.022$), while no significant association of VB12 with Hcy was observed.

VB12 associated biomarker levels according to the severity of neuropathy

Neither VB12, HoloTc nor Hcy differed significantly between patients with mild, moderate, and severe symptoms of neuropathy (Figure 2). Age and diabetes duration were significantly higher in patients with severe neuropathy compared to patients with mild neuropathy.

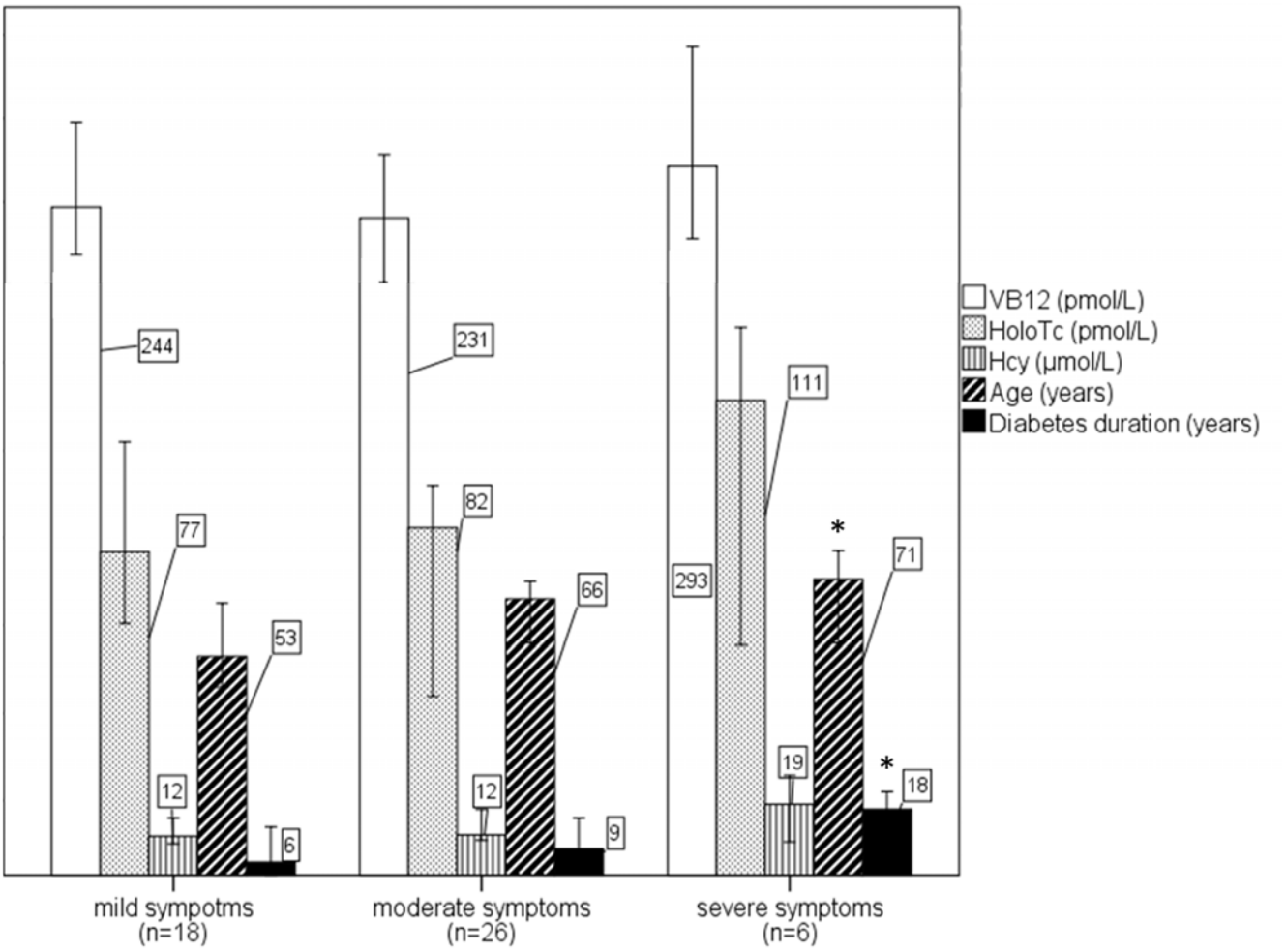


Figure 2: Median levels with 95% confidence intervals of VB12 (pmol/L), HoloTc (pmol/L), Hcy (µmol/L), Age (years) and diabetes duration (years) in patients with mild symptoms, moderate and severe symptoms of neuropathy.

Analysis in patients with low VB12 levels *(sample B)*

LVB12-DM versus LVB12-REF

Diabetes patients with low VB12 (LVB-DM) were compared with a non-diabetic reference group (LVB-Ref). In the LVB-Ref group, a trend towards higher HoloTc level and significantly higher of %AB12 was found (Table 3). Patients in the reference group were younger and had a significantly lower mean BMI (Table 3).

Table 3: VB12 associated biomarker and blood count levels of sample B. Parameters were given as median and 25/75 percentiles, respectively when not otherwise indicated.

	LVB-DM (n=19)	LVB-Ref (n=31)	P-value
Women (%)	50 %	71%	0.22
Age (years)	65 (57/74)	47 (30/60)	0.001
BMI (kg/m2)	29.6 (24.4/34.2)	24.4 (22.6/29.0)	0.02
VitB12 (pmol/L), Roche	162.0 (140/ 178)	164.0 (149/177)	0.75
HoloTc (pmol/L)	53.2 (42.0/ 78.1)	43.0 (32.1/62.2)	0.08
%AB12	32.1 (25.5/48.5)	27.7 (21.5/40.0)	0.04
Hcy (µmol/L)	13.4 (11.0/17.3)	11.9 (9.8/15.3)	0.40
HB (g/L)	134 (131/143)	136 (127/144)	0.98
MCV (fL)	90 (87/93)	92 (90/96.0)	0.74

Prediction of %AB12 in patients with low VB12

A multiple linear regression showed a significant association of %AB12 with diabetes (β=-0.336; p=0.02; r^2=0.092; p=0.023), whilst no significant associations of the %AB12 with age, BMI, renal function expressed as eGFR (Cockroft-Gault) or folic acid levels were observed.

Discussion

In our study neither VB12, HoloTc nor %AB12 differed between T2DM patients regardless of metformin treatment. Median VB12 and HoloTc levels were within the normal range in both groups. Therefore, the primary hypothesis that VB12 levels would differ while HoloTc levels would be indifferent between T2DM patients with or without metformin treatment had to be rejected. Metformin treatment alone did not explain the altered VB12 metabolism as reflected by VB12 and HoloTc serum levels in all T2DM patients, as suggested by the literature [129, 201]. Nevertheless, the proportion of patients in the DMMet+ group with low VB12, low HoloTc, or high Hcy was higher compared to DMMet- group (not significant). Additionally, metformin dosage did negatively correlate with VB12 and HoloTc levels. These findings suggest that metformin may contribute to VB12 deficiency.

Further analysis focused on VB12-deficient subgroups and included non-diabetic patients. In this sample (B), a significant difference of the %AB12 was observed and confirmed by multiple regression analysis. However, the model explained only 9.2% of the variance observed. These results suggest that VB12 metabolism is affected by diabetes itself as well as by other factors, which were not included in the model. It has been proposed that duration of VB12 deficiency and causes of VB12 deficiency play a major role in the VB12/HoloTc ratio [204], such as liver diseases [205] and in particular alcoholism [206]. In this study, patients with liver diseases and/or alcoholism were excluded. Duration of a VB12 deficiency can hardly be assessed in an observational study; therefore, interventional studies might be favorable to continue research on VB12 metabolism. Multiple regression analysis showed that T2DM in general had an impact on %AB12. Further observations regarding the impact of metformin in T2DM patients with low VB12 had a high variance (data not shown) due to the relatively small sample (17 T2DM patients; 11 DMMet+ and 6 DMMet) and therefore were not taken into account. Thus, larger studies may be necessary to differ whether the altered VB12 metabolism is attributable to diabetes in general or specifically to metformin use.

HoloTc has been proposed as a better marker to detect VB12 deficiency compared to serum VB12 [207, 208] in an aged population [209]. We found significant inverse correlations of VB12 and HoloTc with Hcy, a functional marker of VB12 deficiency. Although, the effect was stronger between VB12 and Hcy compared to HoloTc and Hcy, stepwise multiple regression analysis included HoloTc as independent variable to explain variance in Hcy levels and not VB12. Thus, HoloTc seems favorable compared to VB12 to predict hyperhomocysteinemia caused by VB12 deficiency in T2DM patients. Therefore, our results support the finding that HoloTc might be a better marker than VB12 to detect VB12 deficiency. Furthermore, regression analysis showed that

in our sample, elevated Hcy was also explained by age, folate deficiency or renal insufficiency, thus compromising its value as an independent reference for VB12 deficiency. Other studies found inverse correlations between GFR and Hcy within patients with normal renal function also [210, 211]. Metabolism of methylmalonic acid, another functional biomarker of VB12 deficiency, is not affected by vitamin B6 or folic acid. Therefore, measurement of methylmalonic acid might be more sensitive in detecting VB12 deficiency than Hcy. However, methylmalonic acid levels may be compromised in patients with reduced GFR, too [212].

Results from a previous study questioned whether low VB12 in metformin-treated patients with diabetes causes a true or functionally irrelevant cobalamin deficiency [129]. Interestingly, in our study significant inverse correlations of Hcy with VB12 and HoloTc were exclusively found in DMMet+ patients. Meaning that even though VB12 levels were comparable within all DM patients, low VB12 and HoloTc levels did cause functional deficiency in DMMet+ but not in DMMet-. An explanation for this finding might be that no true VB12 deficient DMMet- patients were included in our study, supported by the fact that no HoloTc below 37pmol/L was found in DMMet- group. Furthermore, our data suggest that metformin induces VB12 deficiency in a dose dependent manner. Other studies also found associations between metformin dose and VB12 levels [210, 213]. Thus, it is reasonable to screen patients treated with metformin for VB12 deficiency, as proposed [214]. In a future study, inclusion of anemic patients might help to clarify whether the elevation of functional markers results from of VB12 deficiency or from impaired GFR and whether low VB12 and/or HoloTc coincide with anemia.

VB12, HoloTc or Hcy levels did not differ in patients with mild, moderate or severe symptoms of neuropathy assessed with the NSS and NDS, while, well-established risk factors such as age and duration of diabetes differed between groups. While some studies showed associations between neuropathy, VB12 associated biomarkers, and metformin use [190, 215], others failed to find such correlations [216-218], making results controversial, overall.

Controversy might exist because a range of different assessments for neuropathy and differences in study designs exist. The observed incidence of a VB12 deficiency in this study was high (34%). Irreversible neurologic damage caused by VB12 deficiency is preventable through treatment [130, 190], at relatively low costs, and has few side effects. Therefore, screening for VB12 deficiency independently from diabetic neuropathy seems reasonable.

We acknowledge some limitations. First, our sample size calculation was based on bigger difference in VB12 levels between T2DM patients with and without metformin. However, the prevalence of patients having VB12 deficiency defined as VB12 below 200pmol/L (34% (DMMet+ (39.3%) and 6 DMMet- (28.6%)) we observed is comparable to what is described for elderly users

[219, 220]. Therefore, differences in VB12 associated biomarkers may also be observed within all DM patients when more patients were included. Second, the assessment if HoloTc or VB12 might be better to detect VB12 deficiency was only based on a laboratory marker (Hcy levels). In this study non-anemic patients were included and therefore clinical symptoms where not taken into account. Further studies should include anemic patients and assess methylmalonic acid.

Conclusion

The clinical biochemistry of VB12 in T2DM patients with scarce VB12 supply is modified in comparison to nondiabetic patients. This results in higher %AB12 due to reduced VB12 levels. It needs to be clarified whether this effect is due to diabetes itself, metformin treatment, and/ or a combination of other heath related situations. Assessment of HoloTc seems favorable compared to VB12 to predict hyperhomocysteinemia caused by VB12 deficiency in T2DM patients. This may be a direct consequence of the modified %AB12 in T2DM patients, which strengthens the recommendation to assess VB12 supply in clinical practice by measuring HoloTc. VB12, HoloTc, and Hcy did not differ in patients with mild, moderate or severe symptoms of neuropathy.

Conflicts of interest

The authors declare no conflicts of interests.

Other information

No grants from any external funding body were received to conduct this study.

Acknowledgements

We would like to thank all participating patients and all participating general practitioners and their staff for patient recruitment. We thank Ursula Zoli (Aarelab, Olten) and the laboratory technicians at the Institute of Laboratory Medicine in Olten for their practical contribution. We thank William Caddy for proofreading the manuscript.

7.2 Early Biomarker response and patient preferences to oral and intramuscular vitamin B_{12} substitution in primary care: A randomized parallel group trial [B-2]

Metaxas C[1], Mathis D[2], Jeger C[3], Hersberger KE[1], Arnet I[1], Walter PN[1, 4]

1 Pharmaceutical Care Research Group, University of Basel, Switzerland
2 Division of Clinical Chemistry and Biochemistry, University Children's Hospital Zurich, Switzerland
3 Ring Praxis Olten, Switzerland
4 Institute of Laboratory Medicine, Solothurn Hospitals, Switzerland

Swiss Med Wkly. 2017 April 7;147:w14421.

DOI: 10.4414/smw.2017.14421. eCollection 2017 Apr 19. [136]

Abstract

Background

Treatment of vitamin B_{12} (VB12) deficiency can be performed with oral high-dose substitution of VB12 or by intramuscular (i.m.) injection. Whenever alternative routes of administration exist, patient preferences should be given consideration when choosing the treatment. We aimed at assessing outpatient preferences towards oral or i.m. VB12 substitution and confirming non-inferiority of early biomarker response in the oral treatment of a typical primary care population.

Methods

Prospective randomized unblinded parallel group trial. Patients were recruited by their general practitioner and randomly assigned to oral or i.m. treatment. Group O-oral was given 28 tablets of 1000 µg cyanocobalamin in a monthly punch card fitted with an electronic monitoring system. Group I-i.m. received 4 weekly injections of 1000 µg hydroxocobalamine. Blood samples were drawn before the first administration, after one, two and four weeks of treatment and analyzed for VB12, holotranscobalamine (HoloTc), homocysteine (Hcy) and methylmalonic acid (MMA). For group O-oral, taking adherence and percentage of days with ≥ 2 dosing events were calculated. Before and after 28 days of treatment, patients were asked to fill in a questionnaire about their preference to the therapy options and associated factors.

Results

Between November 2013 and December 2015, 37 patients (age: 49.5 ± 18.5 years; women: 60.5%) were recruited for oral (19) or i.m. (18) treatment. Baseline values with 95% confidence interval for serum VB12, HoloTc, Hcy and MMA were 158pmol/L [145-172], 49.0pmol/L [40.4-57.5], 14.8µmol/L [12.0-17.7] and 304nmol/L [219-390], in group O-oral and 164pmol/L [154-174], 50.1pmol/L [38.7-61.6], 13.0µmol/L [11.0-15.1] and 321nmol/L [215-427], group I-i.m, respectively (p=ns). After one month of treatment, levels of VB12 and HoloTc showed a significant increase compared to baseline (group O-oral: VB12: 354pmol/L [298-410] and HoloTc: 156pmol/L [116-196]; group I-i.m.: VB12: 2796pmol/L [1277-4314] and HoloTc: 1269pmol/L [103-2435]). Further, Hcy and MMA levels showed a significant decrease compared to baseline (group O-oral: Hcy: 13.8µmol/L [10.7-16.8] and MMA: 168nmol/L [134-202]; group I-i.m: Hcy: 8.5µmol/L [7.1-9.8] and MMA: 156nmol/L [121-190]). HoloTc and MMA levels were normalized by all patients at V28, whereas normalization of VB12 and Hcy was reached only by all patients in group I-i.m. Response in VB12, HoloTc and Hcy was more pronounced in group I-i.m. ($p<0.01$) and the primary hypothesis that oral VB12 treatment would be non-inferior to i.m. treatment had to be rejected.

Average taking adherence was 99.6 ± 1.1% and days with ≥2 dosing events reached 5.6%. Before randomization, preference was in favor of oral treatment (45.9%, n=17) compared to i.m. administration (21.6%, n=8). Twelve patients (32.4%) had no preference. Nine (24.3%) patients changed their preference after treatment. Patients who obtained their preferred route of administration maintained their preference in case of oral treatment and changed their preference after i.m. treatment.

Conclusions

Differences in VB12 levels between groups were higher than expected. Therefore, non-inferiority of oral treatment had to be rejected. However, normalization of HoloTc and MMA was reached by all patients after a one-month treatment. The clinical benefit of exaggerated biomarker response after i.m. treatment within a typical primary care population is questionable. Therapeutic schemes should be chosen with the consideration of mid-term biomarker effects and patient preferences. Initial rating in favor of either i.m. or oral therapy can change over time and justifies repeated re-evaluation of patient preferences. (ClinicalTrials.gov ID NCT01832129)

Keywords: vitamin B12 supplementation, vitamin B12 oral, oral versus intramuscular, cobalamin supplementation, patient preferences

Background

Depending on the used definition, prevalence of vitamin B_{12} (VB12) deficiency is between 8-16% and 5-40%, among adults (26-64 years) [221] and in elderly [219], respectively. However, the true prevalence of VB12 deficiency in the general population is still uncertain but is known to rise with age, probably because of an impaired absorption [121, 222].

Causes for VB12 deficiency can be divided into nutritional [223, 224], malabsorption syndromes, and other gastrointestinal causes [223]. Pernicious anemia typically presents with hematological signs and is associated with antibodies to intrinsic factor and/or parietal cells, but accounts for only a small proportion of the observed cases of VB12 deficiency [225]. Furthermore, defective transport mechanisms due to genetic factors account for a very small proportion of the disease [119]. Long-term treatment with acid-lowering agents [226, 227] and metformin [199] may also play a role in the development of VB12 deficiency.

Clinical symptoms of VB12 deficiency are numerous. Besides nonspecific symptoms such as tiredness and a loss of appetite, manifestation of hematologic (megaloblastic anemia), neurologic (e.g. polyneuropathy, ataxia), as well as symptoms of a psychiatric nature (e.g. depression) are possible [119, 130]. Additionally, cardiovascular manifestations which come along with hyperhomocysteinemia are mentioned [186-189]. Because VB12 deficiency is a reversible cause of demyelinating nervous system disease and bone marrow failure, its early detection and treatment are important [130].

Indications for VB12 supplementation is VB12 deficiency with various causes (e.g. pernicious anemia, gastrectomy, dietary deficiency). [130] In addition, preventive treatment should be initiated in pure vegetarians, pregnant women on Mediterranean diet, patients with gastric surgery and Nitrous oxide exposure[122]. However, there are no official threshold concentrations when to initiate treatment. Biochemically, VB12 deficiency is characterized by subnormal to borderline serum VB12 levels. Holotranscobalamine (HoloTc) is the bioactive form of VB12 and has been discussed controversially as a more specific and sensitive marker of VB12 deficiency [124-126]. Functional VB12 deficiency is characterized by an increase of methylmalonic acid (MMA) and/or homocysteine (Hcy). Functional testing is recommended when VB12 deficiency is highly expected, levels of serum VB12 are moderately low (148 to 221 pmol/L), in patients with unexplained macrocytosis or other unexplained neurologic issues and when VB12 deficiency is highly suspected to be the reason for a treatable cause of dementia[122]. Further laboratory

findings are hematological abnormalities such as macrocytosis, pancytopenia and hypersegmented neutrophils. Hematological changes can be found in the more severe cases, while biochemical findings go in parallel with less specific clinical manifestations of VB12 deficiency. However, no clear-cut limits exist for the prediction of symptoms [130]. Subclinical VB12 deficiency occurs and is found in up to 10-25% of the aged population. Treatment of these patients is common, even though the long-term benefits of such treatment are unclear [122].

The treatment of VB12 deficiency consists of VB12 supplementation which can be performed either orally or by intramuscular (i.m.) injections. Patients with severe VB12 deficiency should receive injections of 1000 µg VB12 at least several times per week for 1 to 2 weeks, then weekly until clear improvement is shown, followed by monthly injections [122, 130]. Initial oral treatment with high dose VB12 can be considered in patients with mild malabsorption or dietary deficiency [130] Given the unpredictable absorption of oral treatment, in severe cases, the oral route should only be used after serum VB12 level has been normalized with parenteral treatment or when the response to the treatment is monitored frequently with measurement of serum VB12 and MMA [122] Routine parameters to monitor response to treatment after VB12 substitution are vitamin B_{12} itself , its active fraction HoloTc and either Hcy or MMA as a functional marker (in case of a mild form without hematologic manifestations), and potassium levels, iron status, lactate dehydrogenase and bilirubin (in case of vitamin B_{12} -associated anemia).

In Switzerland, VB12 supplementation is predominantly performed with i.m. injections of VB12 [131], which are usually painful. No high-dose VB12 oral mono-preparation is currently available, despite evidence of its effectiveness [228-230]. Good response to oral supplementation has been observed even in the presence of gastrointestinal diseases that are commonly associated with VB12 deficiency. One study showed that VB12 deficiency could even be reversed in patients who had undergone gastrectomy [231]. However, evidence for the effectiveness of oral high dose VB12 substitution coming from randomized trials comparing oral and i.m. substitution is limited [232].

Oral treatment with VB12 may be superior to i.m. injections in terms of patient acceptance and cost-effectiveness [132]. Patient preferences in treatment-related decisions should be elicited and taken into account, because patients who felt less empowered with regard to treatment decisions reported lower rates of adherence [107]. Finally, a better understanding of patient preferences and values for making choices is fundamental to achieve shared decision making and ultimately improve adherence.

We aimed at assessing outpatient preferences towards VB12 supplementation by oral or i.m. route, and confirming non-inferiority of early biomarker response in the oral treatment in a typical primary care population with biochemically defined VB12 deficiency.

Material and Methods

This prospective, randomized, unblinded parallel-group trial was approved by the ethics committee of the canton Aargau and Solothurn, Switzerland, and has been registered at ClinicalTrials.gov ID NCT01832129. The study was conducted in accordance with the Declaration of Helsinki and follows the International Conference on Harmonization-Good Clinical Practice (ICH-GCP) guidelines. The primary hypothesis was that oral VB12 treatment would be non-inferior to i.m. treatment in terms of serum VB12 response after one month treatment. Patients were expected to prefer oral treatment over i.m. injections before and after a one month treatment.

Participants

Recruitment was initiated at 3 general practitioners (GPs) practices in the area of Olten, Switzerland. Eligible patients had a VB12 serum concentration <200 pmol/l, an indication for VB12 supplementation according to the GP's estimation, were ≥18 years old, and able to give written informed consent. Exclusion criteria were the concurrent intake of vitamin preparations containing VB12, a previously diagnosed dementia, known hereditary transcobolamin transportation defects, or lack of written and/or oral understanding of German, French, Italian, or English languages.

Recruitment

A letter with the patient information and written informed consent form was given to patients whose physician had ordered a laboratory test for the biochemical confirmation of VB12 deficiency. Patients were asked to bring along the informed consent form to their next scheduled visit with their GP during which the results of the lab test would be discussed. Eligible patients were asked by their GP to participate in the study. Patients who gave written informed consent were randomly assigned to group O-oral daily treatment or to group I-i.m. conventional weekly treatment.. Blocks of 4 were generated from computer software. Each GP practice received two blocks (four O-oral group and four I-im-group) each packed in sealed and unlabeled envelopes. Once a patient had consented, the GP or his staff opened one envelope to reveal what group of the study the patient had been randomised to. Upon request, further blocks were available.

Interventions

Patients of group O-oral were instructed to ingest daily one tablet of 1000 µg cyanocobalamine (B12 "Ankermann"; Wörwag Pharma GmbH & Co, Böblingen, Germany) for 28 consecutive days supplied in a 7x4 punch card with electronic adherence monitoring. Polymedication electronic monitoring system (POEMS) technology [33] was used to assess adherence to the oral VB12 intake.

POEMS consist of a film with imprinted electronic components that measure the electrical resistance and record the time of its changes when a loop is broken, i.e. when a cavity is emptied. A first punch card fitted with POEMS was handed out for 14 days. A second identical punch card was handed out for a further two weeks at the third visit two weeks later. Patients were instructed to return the punch cards for pill count and for the extraction of the electronic adherence data. Patients of the group I-i.m. received conventional supplementation with weekly injections of 1000 µg hydroxocobalamine (Vitarubin® Depot 1000 µg / 1ml; Streuli Pharma AG, Uznach, Switzerland, mixed with Lidocaine 1% 1 ml before injection). The treatment options were not blinded.

Adherence outcomes

For a given patient of the group O-oral, we calculated two adherence rates: taking adherence with pill count as the percentage of days with performed intakes divided by the days with prescribed intakes, and dosing irregularities as the percentage of days with ≥2 dosing events from the POEMS data.

Biomarker assessment

Venous blood samples were drawn before the first administration (V0), and after one (V7), two (V14), and 4 weeks of treatment (V28). Blood samples were analysed by immunological assays on a Beckman Coulter DxC 860i (VB12), Roche cobas® 6000 (homocysteine, folic acid), and Abbott Architect i2000SR (holotranscobalamine). Methylmalonic acid was measured by liquid chromatography mass spectrometry (LC-MS/MS) on a Thermo Scientific UltiMate 3000 Rapid Separation LC coupled to an AB Sciex 5500 TripleQuad MS. Blood cell count was determined on a Beckman Coulter DxH 800. Normalization of VB12 associated biomarkers was defined as a serum VB12 >258 pmol/l, HoloTc >37 pmol/l, Hcy <15 µmol/l, and MMA <270 nmol/L. Folate deficiency was defined as a serum value <9.1 nmol/l. GPs were informed about biomarker levels after V28.

Patient preferences

Preferences were inquired before block randomization (V0) and after 4 weeks of treatment (V28) with a scenario-based approach. Patients were asked to select treatment by ticking tablets, syringes, or no preference in a questionnaire, knowing that oral and i.m. substitution was equally effective. The questionnaire consisted of 9 items focusing on factors influencing preference: pain, disgust, side effects, effectiveness, inconvenience, difficulties, time consumption, costs, and non-adherence to treatment schedule. Each item was to be answered twice for each therapy option (oral and i.m. treatment). Answers could be given on a 10-point Likert Scale.

Sample size

Sample size estimation was based on assumptions regarding outcomes after 4 weeks. Patients were expected to display baseline VB12 concentrations of 100–150 pmol/l. Based on published data, patients reach levels of approximately 600 pmol/l with an estimated standard deviation of 120 pmol/l after treatment. A difference of ≤100 pmol/l between levels after intramuscular or oral supplementation was estimated acceptable for non-inferiority, presuming this difference to be clinically meaningless.

With the hypothesis that there is no difference between the groups, 50 patients are required to show with 90% confidence that the lower limit of a one-sided 95% confidence interval will be above the non-inferiority limit of 100 pmol/l.

Statistical analysis

Values are given as mean ± SD, median with quartiles and percentages where appropriate. Frequencies were analyzed using Chi-square tests or Fishers test. Mann-Whitney test was used to compare numerical variables between two groups and Kruskal-Wallis test was used between three groups. Spearman's r was calculated to assess correlations between numerical variables and interpreted with the criteria 0-0.25 = little or no correlation; 0.26-0.50 = small correlation; 0.51-0.75 = moderate to good correlation, and greater than 0.75 = very good to excellent correlation. A *p*-value ≤0.05 was considered significant.

Results

Between November 2013 and December 2015, 37 patients (age: 49.5 ± 18.5 years; women: 60.5%) were recruited for oral (n=19) or i.m. (n=18) treatment. No patient reported on harms or side effects during the study period. Recruitment was terminated after an anticipated analysis showing sufficient biomarker response for both treatment options and enormous difference between groups in mean VB12 values at V28 (2'442pmol/L) leading to the rejection of the primary non-inferiority hypothesis for oral treatment. Post-hoc sample size estimation was based on VB12 outcomes at V28. Patients in group O-oral and group I-i.m. had VB12 levels of approximately 350pmol/L with a standard deviation of 120pmol/l and 2'700pmol/L with a standard deviation of 2'700pmol/L, respectively. With the hypothesis that there is a difference between the groups, a total of 28 patients are required to ensure that the 90% confidence interval includes the true difference between groups with an α of 5%.

The baseline characteristics were equally distributed between the two treatment groups (Table 1). The study population contained patients with the following diagnosis or risk factors associated with VB12 deficiency: pernicious anemia (n=2), metformin intake (n=2), use of acid lowering drugs (n=4), vegetarian or low dietary intake of VB12 containing food (n= 18), diagnosed alcohol abuse or daily intake of alcohol (n=4), and gastric stabling (n=1). No established risk factor for VB12 deficiency was identified in 6 patients. Distribution of risk factors was balanced between the groups (data not shown).

A total of 38 electronic punch cards containing oral treatment were delivered, from which one was not returned (excluded from analysis) and 13 detected only partially the removals due to technical problems. From the 518 expected events, 356 were recorded (31.3% missed data). Days with ≥ 2 dosing event occurred in 5.6% of all recordings. Average taking adherence by pill count was 99.6% ± 1.1%.

Table 1: Baseline characteristics in patients receiving oral or i.m. VB12 substitution (n=37). Data are given as percentages, mean ±SD and median with quartiles.

	Normal values	Group O-oral (n=19)	Group I-i.m. (n=18)	p-value
Women (n)		68.4% (n=13)	55.6% (n=10)	0.508
Age (years)		47.3 ± 17.8	51.5 ± 19.6	0.543
Body mass index(kg/m^2)		27.3 ± 7.00	25.6 ± 4.20	0.715
Vitamin B12 (pmol/L)				
Mean (SD)	>258	158 ± 27.4	164 ± 20.1	
Median (quartiles)		164 (135/177)	161 (152/178)	0.578
Holotranscobalamine (pmol/L)				
Mean (SD)	>37			
Median (quartiles)		49.0 ± 17.7	50.1 ± 23.0	
		49.9 (32.1/63.2)	43.1 (35.8/65.5)	0.940
Homocysteine (µmol/L)				
Mean (SD)	< 15	14.8 ± 5.80	13.0 ± 4.10	
Median (quartiles)		13.2 (10.9/16.7)	13.4 (9.6/16.7)	0.408
Methylmalonic Acid (nmol/L)				
Mean (SD)	< 270	304 ± 172	321 ± 183	
Median (quartiles)		284 (160/379)	249 (183/332)	0.757
Hemoglobin (g/L)	120-160 (women)			
Mean (SD)	135-175 (men)	138 ± 13.1	136 ± 11.8	
Median (quartiles)		136 (127/145)	137 (127/141)	0.822
Mean cell volume (fL)				
Mean (SD)	85-101	91.7 ± 6.40	93.7 ± 6.10	
Median (quartiles)		91 (89/96)	93 (90/95)	0.663
Mean corpuscular hemoglobin (pg)				
Mean (SD)	28-33	30.7 ± 2.10	31.2 ± 2.00	
Median (quartiles)		31 (30/32)	31 (30/32)	0.799
Folic acid (nmol/L)				
Mean (SD)	9.1 - 42.4	16.2 ± 5.80	17.6 ± 5.80	
Median (quartiles)		16.6 (11.8/18.4)	16.7 (13.7/22.0)	0.558
Sodium (mmol/L)				
Mean (SD)	136-145	140 ± 1.9	140 ± 1.7	
Median (quartiles)		140 (139/141)	141 (139/141)	0.775
Potassium (mmol/L)				
Mean (SD)	3.5-5.1	4.6 ± 1.0	4.2 ± 0.3	
Median (quartiles)		4.2 (4.1/4.5)	4.2 (4.0/4.3)	0.298
Creatinine (µmol/L)	49-90 (women)			
Mean (SD)	64-104 (men)	74 ± 14.1	74 ± 12.7	
Median (quartiles)		72 (64/83)	73 (65.25/79.5)	0.916
Alanine amino transaminase (U/L)				
Mean (SD)	<55	8.0 ± 8.6	6.6 ± 5.5	
Median (quartiles)		8.0 (0/11)	6.5 (0/12)	0.964
Aspart amino transferase (U/L)				
Mean (SD)	5-34	25.9 ± 5.9	22.6 ± 3.9	
Median (quartiles)		24 (21/32)	22 (20/25)	0.105
Gamma-glutamyl transferase (U/L)				
Mean (SD)	9-46	39.2 ± 53.2	19.5 ± 10.5	
Median (quartiles)		15 (10/46)	17.5 (10/23.75)	0.916

Levels of VB12, HoloTc, Hcy, MMA, Folic acid (Fol), blood count, sodium, potassium, creatinine and liver enzymes did not differ at baseline (V0) between groups (Table 1). Levels of VB12 and HoloTc were significantly increased at V7, V14 and V28 compared to baseline for both groups ($p<0.01$) (Table 2). For group I-i.m. at each assessment point, VB12 and HoloTc response was significantly higher ($p<0.01$, Figure 1) and the level of Hcy was significantly more reduced ($p<0.01$) compared to group O-oral. Reduction of Hcy levels was significant at V7 for group I-i.m. and at V28 for both groups compared to baseline (group O-oral $p<0.05$; group I-i.m. <0.01). MMA levels were significantly decreased at V7 for both groups compared to baseline ($p<0.01$) and did not differ between groups (Figure 1). Blood count and Fol levels did not change significantly between V0 and V28 in both groups (data not shown).

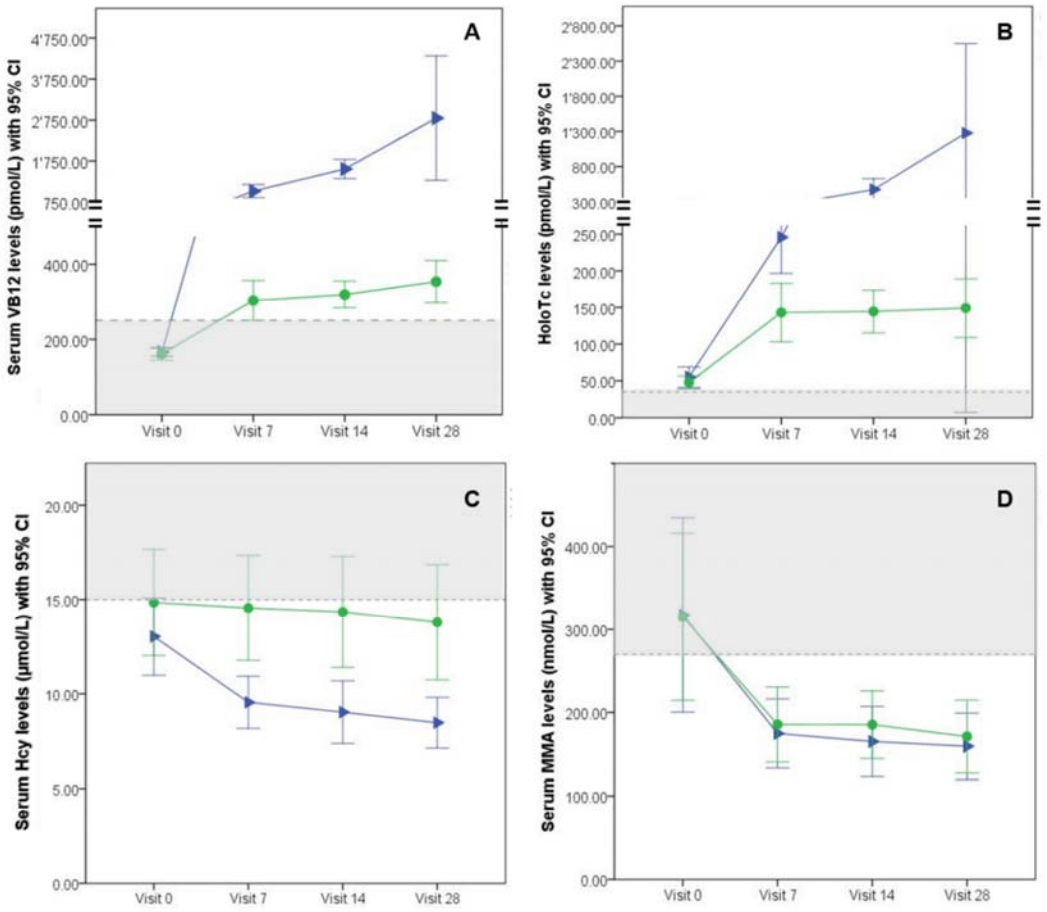


Figure 1: Biomarker levels at baseline (Visit 0), Visit 7, Visit 14 and Visit 28 for group O-oral treatment (●) and group I-i.m. treatment (▶). Grey surfaces indicate sub therapeutic levels, dotted lines indicate threshold values for biomarker normalizaiton. A) Mean serum VB12 levels, dotted line at 258 pmol/L; B) Mean HoloTc levels, dotted line at 37 pmol/L; C) Mean Hcy levels, dotted line at 15 µmol/L; D) Mean MMA levels, dotted line at 270 nmol/L.

Table 2: Mean serum VB12, HoloTc, Hcy and MMA levels with 95% Confidence Interval at V0, V7, V14 and V28 in Group O-oral and Group I-i.m.

		Mean concentration (95% confidence interval)			
	Group	**V0**	**V7**	**V14**	**V28**
VB12 (pmol/l)	**O-oral**	158 (145-172)	304 (250-357)	319 (284-355)	354 (298-410)
	I-i.m.	164 (154-174)	1088 (934-1236)	1897 (1219-2574)	2796 (1277-4314)
	p-value	0.58	<0.001	<0.001	<0.001
HoloTc (pmol/l)	**O-oral**	49.0 (40.4-57.5)	148 (109-187)	144 (115-173)	156 (116-196)
	I-i.m.	50.1 (38.7-61.6)	244 (200-288)	495 (373-617)	1269 (103-2435)
	p-value	0.94	<0.01	<0.001	<0.001
Hcy (µmol/l)	**O-oral**	14.8 (12.0-17.7)	14.6 (11.7-17.3)	14.3 (11.4-17.3)	13.8 (10.7–16.8)
	I-i.m.	13.0 (11.0-15.1)	9.5 (8.2 – 11.0)	9.0 (7.4-10.7)	8.5 (7.1-9.8)
	p-value	0.41	<0.001	<0.001	<0.001
MMA (nmol/l)	**O-oral**	304 (219-390)	188 (148-227)	187 (151-223)	168 (134-202)
	I-i.m.	321 (215-427)	172 (135-208)	161 (127-197)	156 (121-190)
	p-value	0.76	0.53	0.16	0.51

Hcy= homocystein; HoloTc= holotranscobalamine; MMA= methylmalonic acid; VB12=vitamin B12

After 28 days of treatment for group O-oral, normalized VB12 levels were reached by 16 (84.2%) patients, normal Hcy levels by 14 (73.9%) patients and normal HoloTc and MMA levels by 19 (100%) patients (Figure 2). After 28 days of treatment for group I-i.m., all 18 patients (100%) had normal VB12, HoloTc, Hcy, and MMA levels. Percentage of patients with a normalization of all biomarkers at V28 was significantly higher in group I-i.m. compared to group O-oral (100% vs 63.2%, $p<0.05$).

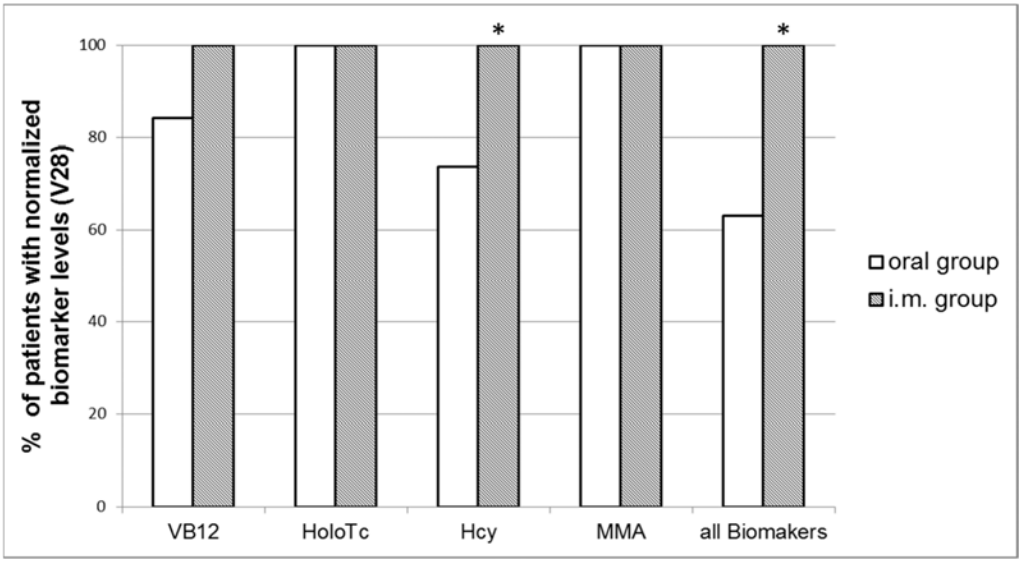


Figure 2: Rate of patients with normalized VB12 associated biomarkers after 28 days of treatment administered by oral (n=19; white bar) or i.m. route (n=18; grey bar), star (*) indicates significant difference = p< 0.05.

At V0, VB12 or HoloTc did not correlate with Hcy or MMA within the study population. Within group O–oral a non-significant small correlation between Hcy levels and VB12 was found at V7 (r-=0.369; p=0.12), V14 (r=-0.388; p=0.10) and V28 (r=-0.341; p=0.15) and between Hcy and HoloTc at V14 (r=-0.397; p=0.10) and V28 (r=-0.392; p=0.10). Levels of VB12 or HoloTc did not correlate with MMA. Within group I-i.m. a moderate correlation was found for VB12 and Hcy levels at V7 (r=-0.725; p<0.001), V14 (r=-0.507; p<0.05) and a small non-significant correlation at V28 (r=-0.254; p=0.38). Levels of HoloTc and Hcy did not correlate nor did levels of MMA correlate with VB12 or HoloTc levels. Correlation between Hcy and creatinine levels was moderate for the whole study population at V0 (r=0.522; p<0.001) and for the group O-oral at V28 (r=0.491; p<0.05). A high correlation was observed for group I-i.m. at V28 (r=0.713, p<0.001).Before randomization 17 patients preferred oral treatment (45.9%), and eight patients preferred i.m. treatment (21.6%).Twelve patients (32.4%) had no preference. Concerns were compared between patients grouped by preference. For the patients who preferred tablets, a therapy with syringes would raise more concerns about the pain (p=0.001), disgust (p=0.004), side effects (p=0.017), inconvenience (p=0.001), difficulties (p=0.001) and time-consumption (p=0.001). Patients preferring i.m. treatment indicated their concerns about forgetting to regularly take the medicine (addressed as non-adherence to treatment schedule) (p=0.018), inconvenience (p=0.024) or higher time consumption when taking tablets (p=0.001) (Table 3).

Table 3: Patients answers to 9 items known to influence preference before randomization. Answers are sorted according to the first question “Which treatment do you prefer?” tablets/ syringes/ no preference. Each item was to be answered twice for therapy with a) syringes and with b) tablets. The higher the score the higher the anticipated effect of the corresponding item on a Likert scale 1-10. Data are given as mean ±SD. P-value <0.05 indicates a significant difference between the group with the highest values versus the group with the lowest values.

Item	Prefers tablets (n=17)	Prefers syringes (n=8)	no preference (n=12)	p-value between three groups
Pain				
a) Syringes	5.7 ± 2.0	3.1 ± 1.6	2.6 ± 1.2	**0.001**
b) Tablets	1.0 ± 0.0	2.1 ± 2.2	1.1 ± 0.3	0.101
Disgust				
a) Syringes	5.9 ± 2.4	3.1 ± 2.2	3.2 ± 2.4	**0.004**
b) Tablets	3.1 ± 1.7	4.6 ± 2.3	2.5 ± 1.4	0.078
Side effects				
a) Syringes	4.2 ± 2.6	2.1 ± 1.8	2.3 ± 1.5	**0.017**
b) Tablets	2.4 ± 1.3	2.8 ± 2.5	2.3 ± 1.5	0.950
Effectiveness of the treatment				
a) Syringes	8.4 ± 1.5	9.0 ± 1.1	8.8 ± 1.3	0.740
b) Tablets	7.8 ± 2.2	6.9 ± 2.3	8.0 ± 1.5	0.454
Inconvenience				
a) Syringes	6.8 ± 1.8	2.6 ± 1.4	2.3 ± 1.2	**0.001**
b) Tablets	2.7 ± 1.5	4.9 ± 2.4	2.3 ± 2.0	**0.024**
Difficulties				
a) Syringes	4.7 ± 2.7	1.8 ± 1.8	1.4 ± 0.7	**0.001**
b) Tablets	1.7 ± 1.7	1.9 ± 1.6	1.3 ± 0.6	0.808
Time consumption				
a) Syringes	7.0 ± 2.6	4.1 ± 2.8	2.4 ± 1.0	**0.001**
b) Tablets	1.2 ± 0.5	2.6 ± 0.9	1.3 ± 0.7	**0.001**
Costs				
a) Syringes	4.5 ± 2.6	3.9 ± 3.1	3.5 ± 2.7	0.503
b) Tablets	2.8 ± 1.7	2.6 ± 1.8	2.4 ± 2.7	0.504
Non-adherence to treatment schedule	3.3 ± 2.6	3.8 ± 2.8	2.6 ± 2.6	0.390
a) Syringes	2.4 ± 2.6	4.3 ± 1.7	2.7 ± 2.9	**0.018**
b) Tablets				

Nine patients (24.3%) changed their preference after treatment. When patients were allocated to the non-preferred administration group, twenty percent of them changed their mind independent of whether they were exposed to p.o. or i.m. treatment: Patients who received oral treatment changed their mind in favor of oral treatment (100%) and patients receiving i.m. treatment changed their mind toward different directions at V28. Patients who preferred oral treatment and were assigned to group O-oral maintained their preference (100% congruence). Patients who preferred i.m. treatment and obtained parenteral treatment changed their preference at V 28 (0% congruence, Figure 3).

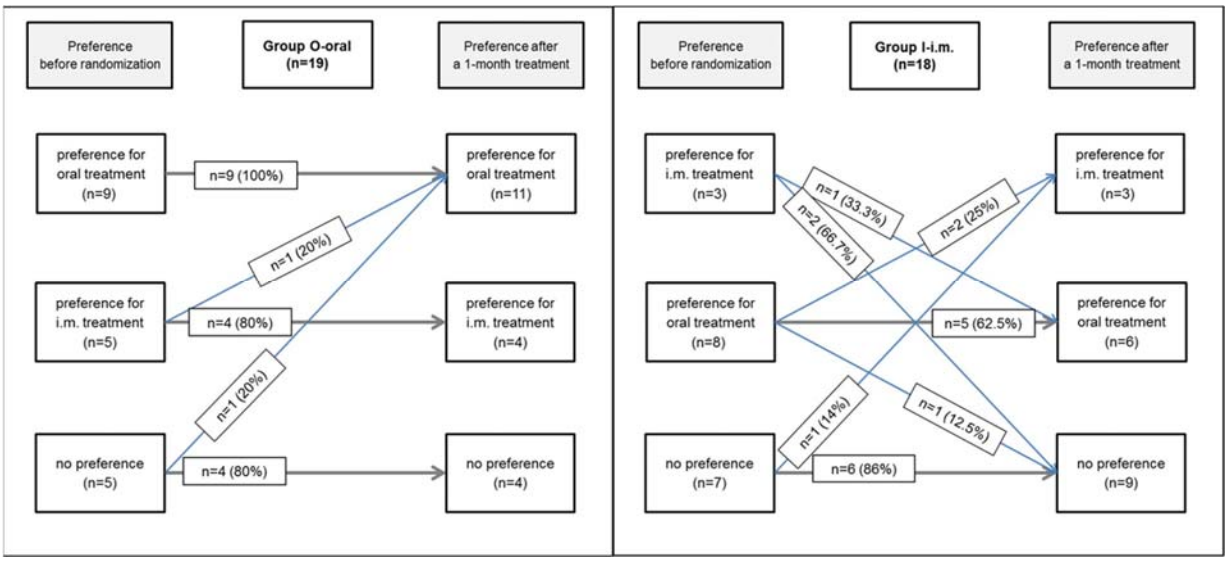


Figure 3: Patients preferences before and after 28 days of treatment administered by oral (n=19) or i.m. route (n=18).

Discussion

In our study, levels of VB12 and HoloTc were significantly increased and levels of Hcy and MMA significantly decreased after 28 days of treatment with high-dose VB12 administered either by oral or i.m. route. These findings are in line with other trials, of which two trials assessed the effect of oral high-dose VB12 substitution (1000 µg cyanocobalamin) vs. placebo [230, 233], while three other randomized, controlled trials compared cyanocobalamin therapy administered by oral (1000-2000 µg) or parenteral route (1000 µg cyanocobalamin) [228, 229, 234].

Contrary to prior studies, we observed an exaggerated response after i.m. administration and therefore the hypothesis for non-inferiority of oral in comparison to i.m. treatment had to be rejected. Because we used electronic punch cards and monitored an almost perfect intake of tablets (99.6% taking adherence), non-adherence can be ruled out as a contributor to the less pronounced response in VB12, HoloTc and Hcy in patients following oral administration. Thus, the enormous difference must have chemical or physiological reasons. One reason might be the use of hydroxocobalamine, a physiological intermediate form which shows a greater availability to cells than other cobalamin forms [235]. In children with VB12 deficiency, one single injection of 400µg hydroxocobalamine resulted in improvement in motor function and cobalamin repletion [236]. Additionally, hydroxocobalamine is longer retained in plasma compared to equivalent doses of cyanocobalamin, which allows less frequent dosing. However, due to its low stability, hydroxocobalamine is less suited for oral supplementation, whereas cyanocobalamin is best suited for oral supplementation due to a more stable and inexpensive form [115]. Surprisingly, sustainability of biomarker response after i.m. hydroxocobalamine administration has poorly been described. In one study among 8 patients with VB12 levels below 80pg/mL (59.4 pmol/L), VB12 levels between 300 and 1100 pg/L (221-812 pmol/L) were obtained 10 days after the injection of 1000 µg hydroxocobalamine. The levels fell below 200 pg/L (148 pmol/L) between 4 and 10 weeks later [237]. In our study, wide inter-individual variation in VB12 and HoloTc responses was observed within the i.m. group, which corresponds to wide inter-individual variations in hydroxocobalamine pharmacokinetics as reported by others [238, 239].

To our knowledge, there are no reports of similarly high levels of VB12 and HoloTc with daily oral VB12 substitution over a longer treatment period, similar to what we observed after i.m. treatment. In one study with high-dose oral substitution of VB12 for 3 months, patients with initially low levels of VB12 (186±56 pmol/L) reached higher VB12 levels (mean 477 pmol/L) than we observed after 28 days of treatment, albeit levels of HoloTc (183 pmol/L), Hcy (13.4 µmol/L) and MMA (0.23 µmol/ 230 nmol/L) were comparable with the levels we observed after 7 days (HoloTc and MMA) and after 28 days (Hcy) of oral treatment [233]. Continuation of treatment up to 6 months did not result in additional significant changes in VB12, HoloTc, Hcy, and MMA [233].

A further study observed a plateau in serum VB12 levels with a mean of 1164 pg/mL (858 pmol/L) after 3 months when patients received a loading dose with 1000 µg hydroxocobalamine and a subsequent 18-month treatment with 1000 µg oral cyanocobalamin [240]. These findings suggest that continuous oral treatment with high dose VB12 reaches saturation in serum VB12 levels after 3 months of treatment. In our study, three patients did not reach normal levels of VB12 after oral treatment. However, two out of those three patients had VB12 levels above normal range at V14, which slightly decreased afterwards. In the absence of any rational explanations (e.g. patients did not stop prematurely treatment) , results indicate that time to VB12 saturation after therapy and the level of saturation may vary between patients. The other patient responded slowly to oral substitution, probably due to the underlying cause of VB12 deficiency, which was gastric stabling (VB12 levels at V0 and V28: 108pmol/l and 182pmol/L). Furthermore, the active part of vitamin B12, HoloTc, was normalized by all patients at V28. Pernicious anemia could be another explanation for non-response in the O-oral group. However, because all patients had some kind of response or a physiological rational for slower response (i.e. gastric stabling), this explanation is very unlikely.

Five patients in the oral group did not reach normalized Hcy levels at V28. However, there is no agreement on normal ranges for VB12 associated biomarkers yet [241]. Hcy lacks specificity and response may be confounded by folic acid and vitamin B_6 deficiency, as well as by renalinsufficiency , liver insufficiency and genetic abnormalities. Additionally, Hcy levels are influenced by, lifestyle, such as consumption of coffee, alcohol, and tobacco [242]. The incomplete normalization of Hcy levels in our cohort could be explained in two patients with folic acid deficiency or diagnosed renal insufficiency, respectively. Additionally, renal function might have affected normalization in other patients as well, indicated by correlation of Hcy and creatinine. Compared to i.m. treatment, decrease in Hcy levels was slower with oral treatment. Other studies also found Hcy levels to respond slowly to oral treatment [230], with a trend to further decrease over a period of 18 months [240].A negative concentration-effect relationship was observed for Hcy and VB12 in the group I-i.m.. A trend towards similar correlation between low Hcy levels and high VB12 levels was observed for group O-oral. A stronger concentration-effect relationship may be observed in patients with a more pronounced deficiency of VB12-associated biomarkers. Before drawing conclusions on concentration-effect relationship between VB12 and Hcy, results should be verified in a bigger sample of anemic patients with consideration of further factors such as renal function and lifestyle.

Interestingly, the functional biomarkers MMA and Hcy did not respond consistently in both groups. Patients in both groups reached normalized MMA levels at V7. Hcy levels in the I-i.m.-group were decreased at V7 too, whereas levels in O-oral-group were decreased at V28, and significantly higher at each assessment point compared to I-i.m. group. The different enzyme systems converting Hcy and MMA in the human body might also explain the observed difference in functional biomarker response between groups. *In vitro* studies showed that hydroxocobalamine induces the activation of one of these enzyme systems (methionine synthase) stronger and faster than cyanocobalamine [243].

In summary, supra-therapeutic levels were observed for VB12 and HoloTc after the i.m. treatment with hydroxocobalamine, which might never be reached through oral substitution. Additionally, normalization of all biomarkers was significantly higher in group I-i.m. compared to group O-oral (100% vs 63.2%, $p<0.05$). However, incomplete response in group O-oral was limited on VB12 and Hcy. Therefore, the benefit of such an exaggerated response after i.m. injection seems limited to a practical advantage in the form of fewer administrations i.e. longer treatment intervals and in case of symptomatic patients needing a rapid normalization of VB12 associated biomarkers. A large prospective randomized controlled trial comparing high dose oral vs intramuscular cyanocobalamin in elderly patients is currently being performed (PMID: 22650964, NCTNCT 01476007). This study is expected to report on long term oral and i.m. VB12 substitution (8, 26 and 52 weeks). However, no reports on short term biomarker response or patient preferences are expected. Further studies are required to assess the effects of different cobalamin forms on biomarker response and on clinical outcomes. Accordingly, observed differences between cobalamin forms should be incorporated in guidelines for treatment of VB12 deficiency.

As expected, patients preferred oral treatment to i.m. treatment, before the assignation to treatment as well as after its completion. Our findings are in line with reports from two studies on patient preferences on oral VB12 treatment [240, 244]. In a study in primary care, 83% of patients preferred over i.m. treatment [240]. In another study, from the patients receiving VB12 as injection and willing to try oral administration, the majority was satisfied with the switch and wished to remain permanently on oral therapy. Important factors for switching to oral therapy were the disadvantage of injections and their association with the many accompanying visits to their respective health care providers, higher costs, and the convenience of oral treatment [244]. We also found time consumption and inconvenience of i.m. treatment as important factors in favor of oral treatment.

There was a slight change in patient preferences after receiving oral therapy (n=2, 10.5%), whilst changes occurred only in favor of oral treatment. This may indicate that patients became appreciative of the route of administration after experiencing oral treatment at first hand. After experiencing i.m. treatment, 11 patients (38.9%) changed their preference in various directions. This is interesting in view of the pretreatment attitudes towards important factors associated with patient preferences, regarding a therapy with syringes (n=6) and regarding a therapy with tablets (n=3). These findings suggest that patients may have more prejudice regarding syringes, which may explain the numerous and various changes after experiencing i.m. treatment.
Given the exaggerated response after i.m. treatment, the required frequency of injections with hydroxocobalamine in clinical practice may be lower, in patients with mild VB12 deficiency, which may augment the preference of an i.m. administration. Additional research with validated methods is needed to gain an insight into the patient preferences, especially when therapeutic options with comparable efficacy and safety are available.

Limitations arrived from the fact that we included patients mostly without hematological symptoms and not necessarily abnormal functional biomarkers. Therefore, patients in our study were less likely to respond to VB12 substitution, what affects our ability to generalize our results to a symptomatic, anemic, VB12-deficient population. Second, the questionnaire we used to assess patients preferences, consisted of re-used questions from several assessment tools but was not validated completely as an entity. Nevertheless, the single questions can be judged valid to retrieve patient preferences. Additionally, we did not assess patient preferences for maintenance therapy and therefore cannot evaluate whether preference would change in this long-term situation. However, it seems justified to reevaluate treatment one month after initiation irrespective of treatment schedule as received treatment is highly suspected to influence attitudes and ultimately patient preferences. Third, we had a high proportion of technical issues leading to a loss of 1/3 of the electronically gained adherence data, therefore days with more dosing events might occurred more frequently as suggested by our calculations. However, this technical drawback had no impact on the calculation of taking adherence with conventional pill count method. Last, we stopped prematurely the study after an anticipated analysis and thus obtained a small sample size. However, the reached normalized levels in both groups did not justify to continue the study since the hypothesis was rejected with the small number of patients.

Conclusion

Differences in VB12, HoloTc and Hcy levels between groups were higher than expected. Therefore, the hypothesis of non-inferiority of oral treatment had to be rejected. However, normalization of HoloTc and MMA was reached by all patients and normalization of VB12 and Hcy by the majority of patients within group O-oral after a one-month treatment. The clinical benefit of exaggerated biomarker response after i.m. treatment within a typical primary care population is questionable. Therapeutic schemes should be chosen with the consideration of mid-term biomarker effects and patient preferences. Initial rating in favor of either i.m. or oral therapy can change over time and justifies repeated re-evaluation of patient preferences. However, the majority of patients preferred oral treatment before and after the study pointing out the need for a high dose oral VB12 preparation in Switzerland. Further research may help to evaluate which route of administration, oral vs i.m., of long-term VB12 treatment, will be appropriate to yield sustained biomarker response.

Acknowledgements

We thank the participating General practitioners and their staff for patient recruitment. The authors thank Jean Pierre Rothen for the initiation of the study, Noortje Vriiends who contributed to the development of the questionnaire to assess patient preferences and Ursula Zoli (Aarelab, Olten) and the laboratory technicians at the Institute of Laboratory Medicine in Olten for their practical contribution. We thank Benjamin Berger for proof-reading the manuscript and Michael Mittag for statistical support.

Funding

No grants from any external funding body were received to conduct this study. Study medication for O-oral group was sponsored by Wörwag Pharma GmbH & Co, Böblingen, Germany and immunologic test kits were kindly provided by Roche Diagnostics (Switzerland), Rotkreuz and Abbott Diagnostics (Switzerland), Baar.

Conflict of interest

The authors declare that they have no conflicts of interest.

7.3 Oral versus parenteral route of application: The patients' perspective [B-3]

Corina Metaxas, Anja Schmutz, Philipp Walter, Kurt E. Hersberger

Pharmaceutical Care Research Group, Department of Pharmaceutical Sciences, University of Basel, Klingelbergstrasse 50, 4056 Basel, Switzerland

Short report

Adapted from the Poster presented at 42nd ESCP symposium on clinical pharmacy: implementation of pharmacy practice; Prague, Czech Republic, 16-18 October 2013.

International Journal of Clinical Pharmacy; December 2013, Volume 35, Issue 6, pp 1251–1351 [137]

Background and objective

Many drugs can be applied either by oral or parenteral therapy. The preferred route of administration is often predetermined by the indication, the required dose and the therapeutic setting. Substitution of vitamin B12 in deficient outpatients is one example where the equivalent efficacy of oral and intramuscular application offers both treatment opportunities. Whenever alternative routes of administration exist, the patient preference should represent a considerable criterion to choose between the treatment options. Our objective was to review current knowledge regarding the patients' preferred route of administration.

Setting and Method

We conducted a literature research in the Pubmed, EMBASE and Web of Science databases using the terms "patient preference" OR "patients' preference" OR "patient perspective" AND "oral treatment" AND "inject*". Our search was limited to original research articles that have been published after 1980, were accessible online and included intravenous, intramuscular or subcutaneous as parenteral therapy options. Cross-references were also included for analysis. The research articles were classified by setting, indication and treatment, number of studied patients and mode of assessment, and patient preference.

Outcome measures

Main outcome was the number of studies with preference for oral treatment. Secondary outcomes included the methods used to assess patient preferences and identified factors with a presumed influence on preference.

Results

Our search strategy delivered 74 articles, of which 62 were excluded (Figure 1). Additionally, one article was included by cross-referencing. Of the gained 13 articles, there were 5 articles on cancer treatment, 3 on antibiotic therapies, 2 on vitamin deficiency, 1 on prophylaxis of thrombosis, 1 on osteoporosis, and 1 on migraine therapy.

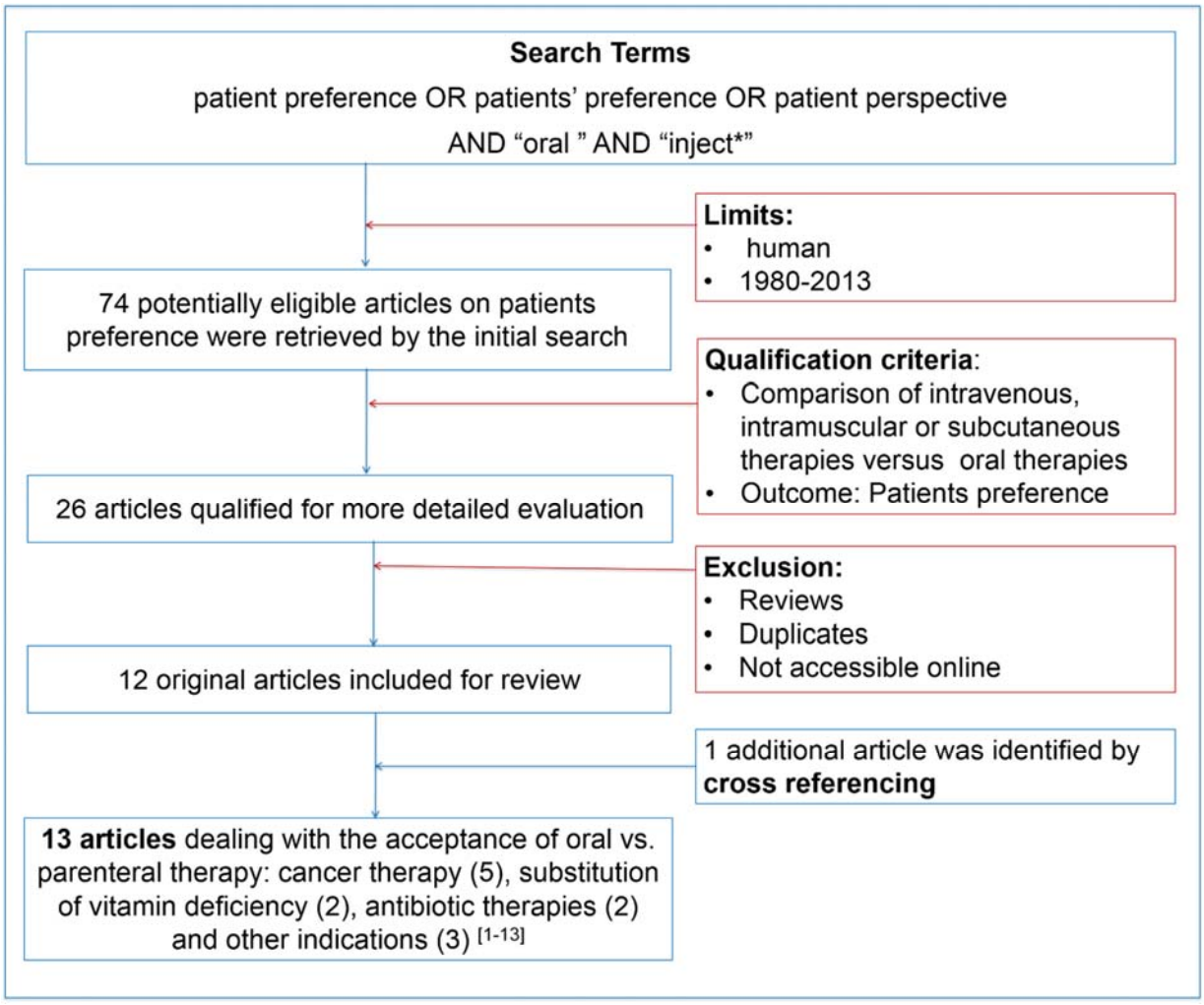


Figure 1: Search methodology and retrieved articles

Eleven out of 13 articles reported preference for the oral administration (84.6%). Associated factors for the preferred routes of administration varied between the studies. Most articles reported convenience as an important factor to influence preference, either in favour of the oral or the parenteral therapy (Figure 2).

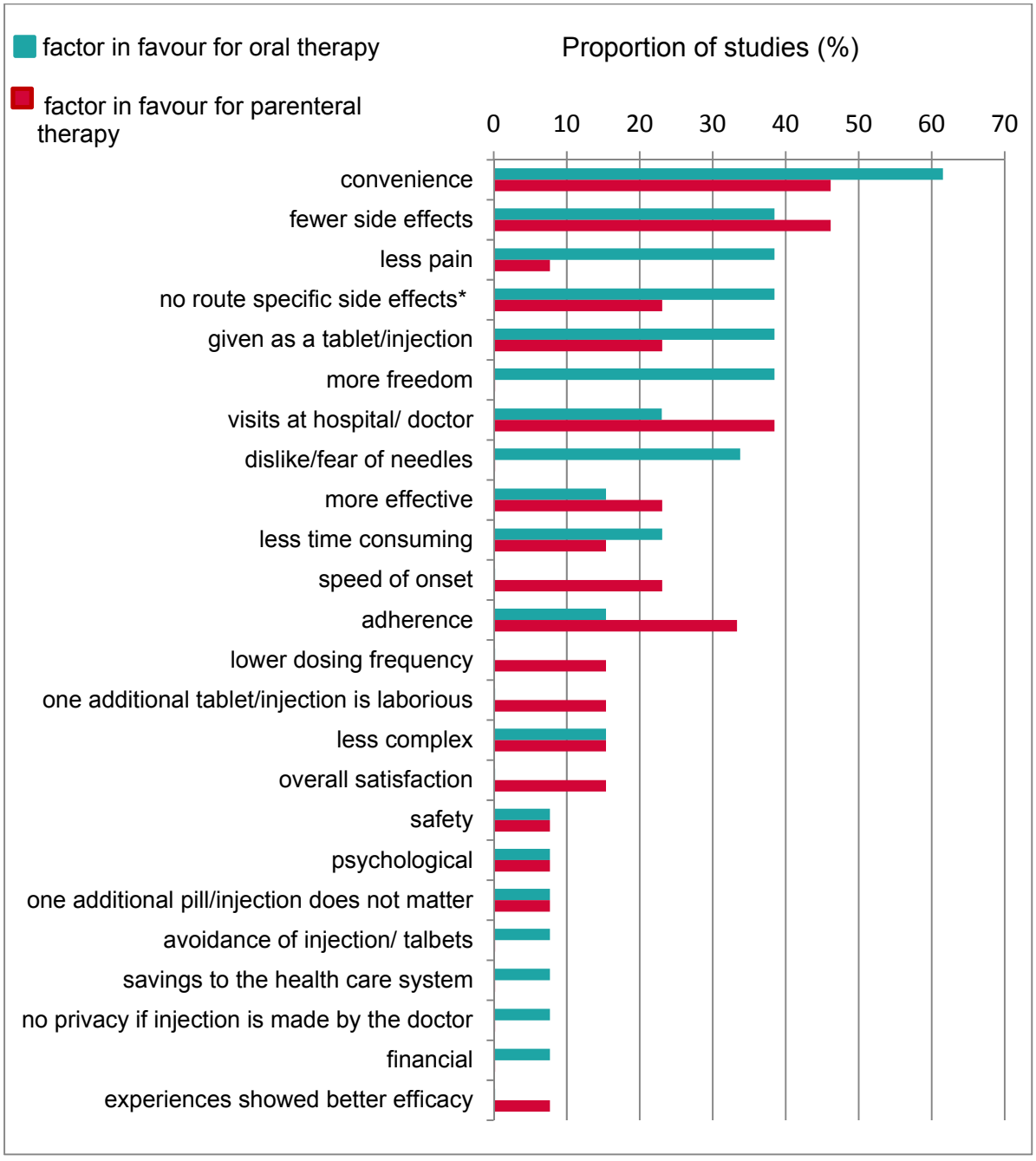


Figure 2: Important factors with a presumed influence on preference
*= injection associated side effects: no infections, hämatoma, problems with veins
*= associated side effects of tablets: no swallowing difficulties, stomach problems

A variety of different questionnaires and study designs were used to assess patient preferences. Two studies used already validated questionnaires to estimate patient preferences (Figure 3). These were an adapted version of the BMQ, the PSQ and one survey based on other studies for which we had not access. All surveys used 5-item Likert scales and one gave 14 options for patients preference. The remaining 11 studies especially designed questions and/or an interview for the study to assess patient preference. Likert-scales (5-10 items) were used 6 times, as often as multiple answer options that were given for factors which influenced patient preference. Three studies either used open questions or only two answer options. Three times scenario-based interviews were carried out either by telephone or in person.

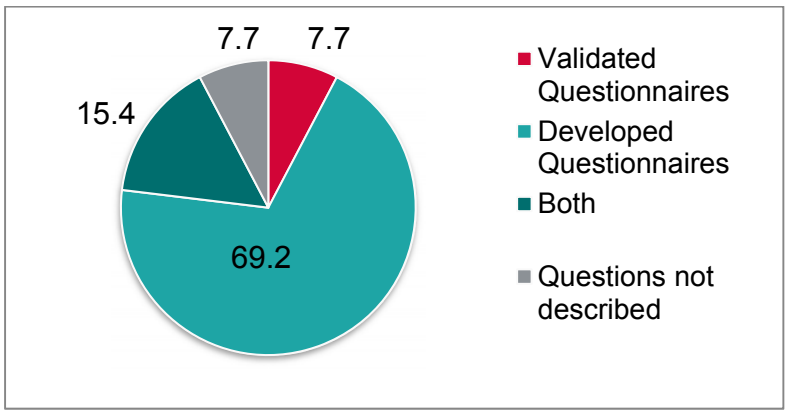


Figure 3: Type of assessment used to measure patient preference [%]

Conclusions

A variety of different questionnaires and study designs were used to assess patient preference. There is a lack of a standardized method, and knowledge about patient preference is still scarce. Unsurprisingly, patient preference for therapy options with identical active ingredient and different ways of application such as oral and parenteral administration (i.e. vitamin B12 deficiency, iron supplementation) is not investigated.

In the retrieved studies, a majority of patients preferred oral treatment. The factor which mostly influenced patient preference was convenience. Dependent on the disease, oral or parenteral therapy was preferred. Given this and the availability of bioequivalent treatments for both therapy regimes, the incorporation of patient preferences may substantially add to treatment optimisation. Patient and physician should take a shared decision concerning the optional therapy regimens in order to promote person individualized therapy and thus, have a major impact on cost-effectiveness.

8 Project C: Adherence assessment methods

8.1 The 8-item Morisky Medication Adherence Scale translated in German and validated against objective and subjective polypharmacy adherence measures in cardiovascular patients. [C-1]

Isabelle Arnet[1], Corina Metaxas[1], Philipp N. Walter[1], Donald E. Morisky[2], Kurt E. Hersberger[1]

1 Department of Pharmaceutical Sciences, Pharmaceutical Care Research Group, University of Basel, Pharmazentrum, Klingelbergstrasse 50, 4056 Basel, Switzerland;

2 Department of Community Health Sciences, UCLA Fielding School of Public Health, 650 Charles E. Young Drive South, Los Angeles, CA 90095-1772, USA

Journal of Evaluation in Clinical Practice 2015 Apr;21(2):271-7.

doi: 10.1111/jep.12303. Epub 2015 Jan 6. [139]

Summary:

Rationale, aims and objectives

To translate in German the 8-item Morisky Medication Adherence Scale (MMAS-8D). To validate it against objective and subjective measures of adherence in cardiovascular patients with polypharmacy.

Method

A standard forward-backward procedure was used to translate the MMAS-8 into German. Validation took place on a convenient sample of ambulatory patients on chronic antiplatelet therapy between June 2010 and June 2011. Objective adherence was obtained from electronically monitored multidrug punch cards. Internal consistency was assessed using Cronbach's alpha coefficient, construct validity using exploratory factor analyses and correlations between MMAS-8D and related measures. Convergent validity was assessed with a subjective questionnaire about beliefs about medicines (BMQ Specific, 2 subscales).

Results

A total of 70 patients were included (mean age 65.7 ± 9.9 years; 31.4 % women). The mean score of the MMAS-8D was 7.5 (SD 0.8; range 4.5-8). Moderate internal consistency (alpha = 0.31) was observed, due to multidimensionality of the scale. Factor analysis yielded four components that accounted for 71.7% of the total variance. Convergent validity was supported by significant correlations with BMQ Necessity (r= 0.31; p<0.01), BMQ Concerns (r= -0.16, p<0.05) and with electronic adherence reports (U-values 44 and 471, p<0.05). Platelet aggregation values were within therapeutic range for 80% of the patients. Blood values of the antiplatelet agent within therapeutic range were associated with a higher MMAS-8D score (U-value 125, p<0.05).

Conclusion

The German MMAS-8 appears to be a reliable instrument to catch medication adherence in cardiovascular patients. It may be useful in patients with chronic therapy for detecting nonadherence.

Keywords: adherence, questionnaire, German version, validation

Introduction

The assessment of medication adherence in patients is crucial as non conformity with prescribed drug regimen poses a substantial risk for therapeutic failure, regardless of the underlying disease [245]. Various adherence assessment methods have been used over the past decades, either direct (i.e., with detection of the substance in a biological fluid, thus proving that a dose of a drug was ingested) or indirect (i.e., which do not demonstrate drug ingestion). From the indirect measures (such as self- reporting, medication diaries, residual pill counting, pharmacy records, clinician opinion, electronic devices with remote control), questionnaires remain the most commonly used type because of major advantages (mainly they are simple, practical, cheap, non-invasive, unobtrusive) [246], while electronic monitoring represents the most objective measure [247].

Among self-reported questionnaires, the 8-item Morisky Medication Adherence Scale (MMAS-8) [24] is one of the most widely used scale to measure self-reported adherence, mainly because of the simplicity of its administration and scoring. It consists of seven yes/no questions and one 5-point Likert scale. The scale has demonstrated high internal consistency and good sensitivity and specificity; it was shown to be valid and reliable [24]. The questionnaire was shown to be an effective screening tool in clinical practice to identify non-adherent patients at risk of uncontrolled blood pressure [248]. The MMAS-8 has been translated into more than 50 languages, e.g. French, Malay, Portuguese and Thai [29, 249-251] and used in long-term medical conditions, across different settings and various cultural contexts. The scale has also translated into Chinese and analyzed with hypertensive and myocardial infarction patients [252, 253].

Numerous adherence studies have been conducted in a German speaking setting, most of them with self developped questionaires [254] or scales [255]. Parts of the MMAS-8 have been translated in German and used in specific investigations [256] or larger trials [257] but the German scale was never validated. Consequently, one can assume that several German versions of the psychometric instrument are available, rending comparison of results questionable. Further, the lack of validation might lead to biased results. Adherence to antiplatelet therapy has been estimated in many studies and appears to be high. Of 2,640 patients surveyed in the German Stroke Data Base, 96% reported to be still on any antiplatelet therapy (mostly aspirin) for prevention one year after their stroke [258]. In a retrospective analysis using administrative claims data of 9,635 US veterans with established cardiovascular disease, 84% had sufficient antiplatelet medicine dispensed over 5 years to cover 80-120% of the treatment duration [259]. Considering that interventions aimed at optimizing adherence will be more effective if they are tailored to a

patient´s needs, health professionals will need on one hand overall adherence measurement tools, on the other hand single items assessing pre-existing behaviours and habits. Because of the foreseeable use of the MMAS-8 as an adherence measurement and assessment tool in German speaking countries including Switzerland, we were interested in establishing a German version of the MMAS-8, the MMAS-8D (Deutsch).

The validity of electronic devices (i.e. systems that record date and time of each dispensing of medication) in measuring adherence was demonstrated in many studies, either for container caps with single drug [260] or for weekly pill boxes with polypharmacy [261]. Recently, electronic monitoring was recommended as method of choice in research on adherence [262]. A meta-analysis demonstrated a high to moderate correlation between self-reported questionnaires and medication adherence measured using monitoring devices [263]. Thus, we performed a validation against electronic measures of adherence and the Beliefs about Medicines Questionnaire [264], a validated subjective questionnaire which showed a significant relationship with adherence to medication in substantial different social, cultural, economic and healthcare system contexts [247]. Further, the association did not differ if objective or subjective adherence measures were used. This article reports the validation of the German MMAS-8 against objective and subjective measures of adherence in ambulatory patients with antiplatelet therapy.

Method

Participants and setting

A convenient sample of 19 general practitioners in Solothurn, Switzerland, invited patients with chronic antiplatelet treatment to participate in a cross-sectional study on drug resistance between June 2010 and June 2011. The study is described elsewhere [265]. In brief, 82 outpatients older than 18 years with on-going prescriptions for aspirin and/or clopidogrel accepted participation. They obtained their entire oral solid medication (polypharmacy) for seven days in a punch card equipped with electronic adherence monitoring. Blood samples were collected after adherence monitoring to measure platelet aggregation and to determine polymorphism of the CYP2C19 gene. The patients were aware of the purpose and function of the electronic system prior to study. They were advised to take their medicine at the time they were normally used to, by just pushing out all the pills contained in one cavity. Filling of the questionnaires was performed at the study center, questions were answered on site by the study investigator. This observational cross-sectional study obtained ethical approval from the Swiss local ethics committee of Aargau and has been registered at ClinicalTrials.gov ID NCT01039480. All patients provided written informed consent before participation.

Translation of the instrument

Translation in German was done according to the “Principles of Good Practice” for the translation and cultural adaptation process for patient-reported outcomes (PRO) measures [266]. The back translation technique was performed by two translators, one conducting the forward translation and the other one conducting the back translation. Equality of sense rather than equality of word was favoured. The source language versions were compared and discrepancies lead to modifications in the target language version until both translators were satisfied with semantic and conceptual equivalence between source and target languages. The developer of the MMAS-8 approved the German version. The corrected target language version was validated with 3 monolingual subjects for comprehensiveness, appropriateness, acceptability, and feasibility.

Subjective adherence measure

The MMAS-8 [24] consists of seven yes/no questions and one 5-point Likert scale. Patients answering “no” to all questions but ‘‘yes’’ to item 5 (reverse coding) and “Never/rarely” to item 8 obtain the maximal 8 points and are classified as “high adherence”. Patients answering differently obtain a lower score that indicates lower adherence and are classified as “medium” (6-<8) or “low” (<6) adherence. The questionnaire takes about 5 minutes to complete. The term “[health concern]” medication was not specified in our questionnaire in order to steer for polypharmacy.

Beliefs about medicines

The Beliefs about Medicines Questionnaire (BMQ) [264] is an instrument that assesses the cognitive representation of medication and consists of two sections (BMQ-Specific and BMQ-General). Many studies demonstrated a high correlation between BMQ scales and self-reported adherence in several chronic diseases, including asthma [267], hypertension [268], HIV [269], and diabetes [270]. We selected this questionnaire since it targets beliefs about medicine in general, i.e. polypharmacy, and not a single drug. The German version has been validated in chronically ill patients and showed good internal consistency (Cronbach's alpha 0.79–0.83).[271] We used the BMQ-Specific that assesses patients' beliefs about the particular medication prescribed for them and consists of a 5-item Necessity scale (necessity of taking medications for maintaining present and future health) and a 5-item Concerns scale (concerns about the potential adverse consequences of taking medicine). Responses are given on a 5-point Likert scale ranging from strongly agree (scored 5) to strongly disagree (scored 1). Scores are summed and range from 5 to 25 for each subscale, with high scores indicating strong beliefs in the concept. The Necessity-Concerns differential is calculated by subtracting concerns scores from necessity scores (scores range from -20 to 20). This score represents a crude indicator of the way a person rates his/her perceived need for the treatment relative to his/her concerns about following it. If the differential is positive, the person notes that the benefits of medication outweigh the costs. Contrarily, if negative, the person perceives heavier cost than benefit [264].

Objective adherence measures

Polypharmacy electronic monitoring system (POEMS) technology [246] was used to asses adherence to the reference medication. In brief, POEMS consists of a polymer film with imprinted electronic components that measure the electrical resistance and record the time of its changes when a loop is broken i.e., when a cavity is emptied. The patient's entire oral solid medication is filled in a disposable multidrug punch card with 7x4 cavities, equipped with the film on its backside. For a given patient, we calculated two established adherence rates to the antiplatelet agent i.e., to the drug of interest within the prescribed polypharmacy: taking adherence (number of days with performed intakes divided by number of days with prescribed intakes) and timing adherence with the strictest grace interval of 25%[272] (number of doses taken at 24 ± 6 hours for a once-daily regimen or 12 ± 3 hours for a twice daily regimen). In addition, we calculated for each patient the mean drug intake time of the antiplatelet agent. The timing variability in drug intake was defined as variance of the mean drug intake time[273] and indicates the timeliness of the intakes.

Platelet aggregation was measured in venous blood samples and is described elsewhere [265]. In brief, values below the cut-off of 30 arbitrary units (AU) for the ASPItest (Aspirin) and 53 AU for the ADPtest (clopidogrel) were considered as in the therapeutic range and consequently, the patient as fully adherent. Pharmacogenetic analysis of the CYP2C19 gene was performed for clopidogrel values outside therapeutic range. Polymorphism (CYP2C19*2, 2C19*4, 2C19*17) is associated with insufficient platelet inhibition in clopidogrel-treated persons [274]. Laboratory signs of inflammation were defined by C-reactive protein >5 mg/l and is associated with resistance to Aspirin [275].

Statistical analysis

Where appropriate, mean and standard deviations, median and interquartile ranges are presented. Internal consistency or reliability of the MMAS-8D was assessed using Cronbach's coefficient alpha which indicates whether each item of a scale is appropriate for assessing the underlying concept of its scale. Values for Cronbach's alpha range between 0 and 1; the closer they are to 0, the less the items are related to one another. Values above 0.7 are generally considered to indicate satisfactory internal consistency [276]. However, opinions differ regarding acceptable cut-offs [277].

Construct validity i.e., the degree to which an instrument reflects the underlying construct that it was designed to assess, was performed with exploratory factor analysis (principal component analysis extraction method, PCA), followed by varimax rotation. Factors with Kaiser's eigenvalues of >1 were selected i.e., factors that accounted for more of the total variance than any single original item. Factor loadings greater than 0.4 were used for defining items associated with a given factor. Results are given in terms of percentage of variance in the score explained by the principal factor.

Convergent validity i.e., the degree to which an instrument is related to measures of similar constructs, was performed with the non-parametric Spearman's rho test since self-reported values (MMAS-8D and BMQ-Specific) and objective measure (electronic punch cards) were skewed toward high scores. Differences in adherence rates were compared using the Mann–Whitney *U* test for continuous variables, comparison of categorical variables was performed with Chi-Square test. Correlations were interpreted with the criteria 0-0.25 = little or no correlation; 0.26-0.50 = small correlation; 0.51-0.75 = moderate to good correlation, and greater than 0.75 = very good to excellent correlation. Data were entered and analyzed using SPSS statistical package version 21.0 (SPSS Inc, Chicago, Illinois, USA) and p-values <0.05 were considered significant.

Results

From 82 enrolled patients, 12 were excluded because of missing data due to deficiency in the recording technology. Of the remaining 70 patients (mean age 65.7 ± 9.9 years; 31.4% women, mean age 67.9 ± 9.7 years and 68.6% men, mean age 64.7 ± 9.9 years; n.s.) full sets of data were available. The study sample consisted of patients with a prescription of antiplatelet agents for primary (42.9%) or secondary prevention (57.1%). Mean number of prescribed drugs per patient was 5.2 ± 2.3 (range 1-13) that were to be taken once daily (37.1%; all but one in the morning), twice daily (48.7%, all but four in the morning and the evening), thrice daily (11.5%) or fourth daily (2.9%). With one exception, all antiplatelet agents were lodged with the morning medication (98.6%). All doses of the antiplatelet agents were taken (100% taking adherence) and all but 4 patients had intake times within the grace interval of ± 3 hours (91.4% timing adherence). A stricter grace interval of ± 1.5 hours was observed in 39 patients. The variance of the mean intake times averaged 1.4 h^2 ± 4.3 h^2, with a median of 0.5 h^2 and an interquartile range IQR of 0.8 (25^{th} percentile of 0.2 h^2; 75^{th} percentile of 1.0 h^2). The variance was not associated with the number of drugs (r= 0.19; p=0.06; n.s.) nor with the number of intake times (r= 0.17; p=0.08; n.s.). Platelet aggregation values were within therapeutic range for 74% of the patients taking aspirin, 75% of those with clopidogrel and 95% of those on dual therapy, yielding to total 56 patients (80%) with optimal platelet aggregation. For further 7 patients (10%), genetic mutation (3 patients with clopidogrel) or underlying inflammation factors (4 patients with Aspirin) were detected.

Responses of the MMAS-8D were coded analogue to the English version. With the recommended scoring method, the mean score of the MMAS-8D was 7.5 (SD 0.8; range 4.5 - 8), with a median of 8 and an interquartile range IQR of 1 (25^{th} percentile of 7; 75^{th} percentile of 8). With the recommended cut-offs, the majority of patients were in the high adherence group (64.3%), while 30.1% and 5.7% were in the medium and low adherence groups, respectively. Only 2 patients indicated that they did not take their medication the day before (item 5) while 9 patients (12.9%) declared to forget sometimes to take their medication (item 1). The mean BMQ scores were 19.7 (SD 4.1; range 6 – 25; median 20) for the Necessity scale and 9.5 (SD 3.9; range 5 – 20; median 9) for the Concerns scale. With a Necessity-Concerns differential of 10.1 (SD 5.6; range -2 – +20), participants noted that the benefits of medication outweigh the costs.

Internal consistency / Reliability

Cronbach's alpha was 0.31 for the eight items of the German version MMAS-8D and slightly higher when item 1 was not used for computation (0.40). Overall standardized Cronbach's alpha was 0.41. The item-to-total correlations ranged from -0.015 to +0.530 (Table 1).

Table 1: Reliability test (n=70)

	Corrected item-total correlation	**Cronbach's alpha if item deleted**
Item 1	-0.015	0.401
Item 2	0.287	0.161
Item 3	0.127	0.282
Item 4	0.064	0.309
Item 5	0.009	0.328
Item 6	0.038	0.317
Item 7	0.247	0.219
Item 8	0.530	0.202

Construct validity

The principal component analysis (PCA) was used to show the dimensionality of the scale. On the basis of eigenvalues greater than 1, four components were retained, which explained 71.7% of the total variance. The items that contributed to the first component involved forgetfulness and remembering (items 1, 2, 8) and explained 24.4% of the variance. The items that contributed to the second component (17.3% of the variance) concerned stopping medication when one feels better and feeling hassled about one's treatment plan (items 6, 7). The items that contributed to the third component concerned stopping medication when one feels worse and taking the medication the day before (items 3, 5). Item 4 concerning travelling situation contributed to the fourth component (13.5%). Table 2 shows the moderate to strong loading (>0.4) of all items, after varimax rotation with Kaiser normalization.

Table 2: Items, patients' answers and maximal value of factor loading of the MMAS-8D in German (n=70)

Item nb.	Patients' response to be considered adherent	Number (%)	Factor loading (component)*
1	No	61 (87.1%)	0.692 (1)
2	No	64 (91.4%)	0.179 (1)
3	No	64 (91.4%)	0.748 (3)
4	No	67 (95.7%)	0.875 (4)
5	Yes	69 (98.6%)	0.795 (3)
6	No	68 (97.1%)	0.782 (2)
7	No	67 (95.7%)	0.824 (2)
8	Never/rarely; Once in a while; Sometimes; Usually; All the time	Never: 62 (88.6%) Once: 7 (10%) Sometime: 1 (1.4%)	0.773 (1)

* first, second, third or fourth component obtained with principal component analysis (PCA) after varimax rotation with Kaiser normalization

Convergent validity

Convergent validity of the MMAS-8D was demonstrated through correlations with objective and subjective measures (Table 3). Patients with intake times within a grace interval of ± 3 or 1.5 hours had a significant higher MMAS-8D score (U-values 44 and 471, $p<0.05$). Adherence measured as timeliness of the intakes correlated moderately with MMAS-8D scores ($r= -0.15$) and in the expected direction, without reaching statistical significance ($p=0.11$; n.s.). There was a statistically significant relationship between items 6 and 7 and the recorded intake times (Chi-Square value 34 and 22, $p<0.01$), with patients not stopping their medicine when they feel like their health is under control (item 6) and not feeling hassled about sticking to their treatment plan (item 7) taking their medication more often within the 3 hours grace period. The MMAS-8D scores were significantly correlated with the Necessity ($r= 0.31$; $p<0.01$) and the Concerns subscores of the BMQ questionnaire ($r= -0.16$, $p<0.05$). The correlations were small to moderate and in the expected directions i.e., patient who self reported higher adherence to their medication with the MMAS-8D had significantly higher sense of necessity of medication and lower concerns about it. After exclusion of the 7 patients with inflammation or genetic polymorphism, blood values of the

antiplatelet agent within therapeutic range correlated highly with MMAS-8D score (U-value 125, $p<0.05$). A subgroup analysis was performed according to indication of antiplatelet therapy. Patients with an antiplatelet agent for secondary prevention showed a statistically significant higher MMAS-8D score than patients in the primary prevention group (median 8 vs 7; U-value 407, $p<0.01$).

Table 3: Convergent validity: Spearman correlations and Mann-Whitney-U values of the MMAS-8D with objective adherence measures (electronic monitoring and blood values of antiplatelet agent) and beliefs about medicine scores

	MMAS-8D		
Measures [numbers of patients]	Correlation	U-value	p-value
BMQ necessity [70]	0.31		<0.01
BMQ concerns [70]	-0.16		<0.05
Adherence as timeliness of intake [70]	-0.15		0.11 (n.s.)
Adherence as variability ± 3 hrs [70]		44	<0.05
Adherence as variability ± 1.5 hrs [70]		471	<0.05
Platelet aggregation in the range [63]		125	<0.05

Discussion

In the present study with electronic adherence monitoring as reference standard, we examined the reliability and validity of the 8-item German version of the Morisky Medication Adherence Scale. The high adherence scores obtained electronically even with the strictest grace interval for medication intake were indicative of a highly adherent sample of patients. Direct measure of adherence by laboratory tests like platelet aggregation confirmed drug intake for 80% of patients, while reasons for reduced antiplatelet effect like genetic polymorphism or inflammation were observed for further 10% of the patients. Estimates of adherence obtained with the translated scale were in concordance to all rates calculated from electronic records.

We found for the German version of the MMAS-8D low psychometric properties compared with the original English MMAS-8, especially for internal consistency (Cronbach's alpha 0.31 vs. 0.83.[24]) The small to moderate reliability we observed is similar to that of three other studies that validated the French [251], Malaysian [29] and Thai [250] versions of the MMAS-8. Since Cronbach's alpha measures whether each item of a scale is appropriate for assessing the concept of the scale, the internal consistency of the entire scale will be high if all items measure the same phenomenon. In our case, we retained 4 components after varimax rotation that explained 71.7% of the variance (24.4% for the first component), indicating that the scale is four-dimensional. This is in contradiction with the original English scale that was declared one-dimensiona l[24], but in strong concordance with the results of the French and the Thai scales that attributed 55.2% and 57.4% of the variance, respectively, to three components [250, 251]. Consequently, the unacceptable low Cronbach's alpha in our study may indicate the multidimensionality of the scale rather than its inconsistency [277]. Further, the MMAS-8 contains items aimed at identifying *reasons* for non adherence that can be classified as causal indicators rather than effect indicators [278]. Because causal indicators by definition may not be highly intercorrelated, statistics with Cronbach's alpha are inappropriate for these indicators, since high internal consistency depends on high inter-item correlation [278]. In this sense, some authors urge to indicate supplementary information to evaluate multiple-item measures of a scale [277] since Cronbach's alpha seems to be an inadequate index to describe the internal consistency of a scale.

Although subjective and objective measures of adherence have different strengths, the MMAS-8D demonstrated convergent validity with electronic measures of adherence and with laboratory values. Since subjective measures are subject to potential inaccuracy because of patients' memory or reluctancy to report deviant behaviour, and may thus overestimate adherence [279], objective measures with electronic systems were valued as more accurate. However, the correlation between self-related questionnaires and electronic records of adherence was shown to be small to moderate [263], predominantly because different sets of information are collected

with different approaches and perspectives. Notwithstanding, the correlation with electronic records, blood values and the significant association with BMQ subscores support the validity of the MMAS-8D. The latter is in accordance with findings from a study with women newly treated against osteoporosis with daily or weekly oral bisphosphonates, where the Necessity subscore of the BMQ showed a significant association with the 8-item Morisky scale [280].

The subgroup analysis showed that patients with antiplatelet therapy for secondary prevention self-reported a higher adherence than patients in primary prevention. This is in line with a recent meta-analysis with 376,162 patients, where 2/3 of the patients with a history of cardiovascular disease (and thus with a prescribed drug to prevent secondary disease progression) were adherent, compared to 1/2 of the patients with a drug to prevent a first event (primary prevention) [281].

The authors acknowledge some limitations of the study. First, the sample could be prone to selection bias. Motivated patients might have been more likely to accept participation and thereby be more adherent than the general population of outpatients with antiplatet therapy. In a similar perspective, the sample could be prone to social-desirability response bias i.e., patients tending to present themselves in the most favorable manner. This is suggested by the overrepresentation of the maximal MMAS-8D scores, with almost 2/3 of the patients allocated to the high adherence group. This substantial ceiling effect is common in questionnaires [282]. Similar high results were observed in the French validation study (median score of 7; 44% of patients in the high adherence group.[251]) Second, the modest sample size may have biased our results, since small sample sizes can affect the result of the internal consistency. However, our sample size was greater than the study validating the Swedish version of the MMAS-8 (60 respondents in 1998, 53 respondents in 2002[283]) and than the first study validating a rating scale against electronic monitoring (61 patients with electronic medication's caps [284]). Third, the relatively brief monitoring period may be criticized because insufficient to estimate overall adherence to therapy. However, given that firstly intake of an antiplatelet agent over seven days is sufficient to influence platelet aggregation and to be detected in blood, and that secondly MMAS questions span the past 2 weeks, the short study period was estimated satisfactorily in our validation setting and able to deliver the required values of intake pattern. It should be further mentioned that the validity of the MMAS-8D scale might be somewhat compromised when the single medication for the health condition is not specified in the scale item. However, this health concern specified item is not compatible with polypharmacy and consequently, we generalized the items to target polypharmacy and not a single drug. By doing so, we made the items agree with the electronic monitoring. Finally, any electronic monitoring device can act as intake reminder and temporarily enhance adherence,

especially when participants are aware of the purpose of the electronic system as in our study. However, a recent randomised controlled trial with 226 diabetes patients investigated the reactive effect of electronic monitoring over 8 weeks [262]. The authors concluded that using an electronic device may lead to a small increase in adherence compared to standard packaging, however without reaching significance and without changing over time. As a consequence, a slightly higher adherence is inevitable in a patient's population equipped with any reminder packaging.

Because the German language is the official language in Germany, Switzerland and Austria, with identical grammar and orthography, our questionnaire can be used in the 3 German speaking countries without further adaptation. We could not find any negative comments in the literature when a questionnaire in German is used in several German speaking countries. A recent survey was developed in Switzerland in German language and was sent simultaneously to nurses in Switzerland, Germany and Austria through their respective societies [285]. The authors did not mention any comment on the language of the questionnaire. Much more, an international multicentre validation of a newly translated questionnaire in German was approved by ethic committees in Switzerland, Germany and Austria and was a strength for the recruitment of patients in primary care [286]. Cultural differences between the German speaking countries may concern the health system, which however is not a topic in the MMAS.
To conclude, the German MMAS-8D was able to categorise 94.4% of the patients as good adherer, which was confirmed by established measures of adherence obtained from electronic data. It appears to be a reliable instrument to catch medication adherence in cardiovascular patients, despite a low internal consistency. Further, it is endowed with simplicity and quickness of administration and scoring, which facilitates its use in several pathologies.

Acknowledgments
We wish to thank Dr. Michael Mittag for statistical support.

Author contributions
The work presented here was carried out in collaboration between all authors. IA and KEH defined the research topic. PNW and IA designed the methods and the instruments. PNW carried out the study. CM analysed the data. IA interpreted the results and wrote the first draft of the manuscript. DEM discussed the analyses and the interpretation. All authors have contributed to, reviewed and approved the manuscript.

Copyright licence statement

8.2 Medication possession ratio may detect half of the self-declared non-adherent patients to direct oral anticoagulation treatment – A pilot study [C-2]

Metaxas C, Hersberger KE, Arnet I

Pharmaceutical Care Research Group, Department of Pharmaceutical Sciences, University of Basel, Klingelbergstrasse 50, 4056 Basel, Switzerland

Short report

Adapted from the Poster presented at the 10th Pharmaceutical Care Network Europe (PCNE) Working conference: Build- Lead- Engage- Disseminate Bled, Slovenia, 1-4 February 2017.

International Journal of Clinical Pharmacy; June 2017, Volume 39, Issue 3, pp 601–626 [140]

Background

Poor adherence to direct oral anticoagulants (DOAC) treatment in practice has been reported [287]. Because of non-forgiving characteristics, DOACs require strict intake intervals that translate into very high adherence rates. Identifying deviant behavior is needed to initiate adherence counselling. Indirect measures can be used to detect non-adherence such as self-report (subjective) or pharmacy refills (objective). The Polymedication Check (PMC) is a reimbursed intermediate medication review in Switzerland that focuses on adherence and medicines use in outpatients. The PMC consists of a semi-structured interview covering one closed-end question on adherence (subjective measure). In Switzerland, dispensed packages, daily prescribed doses and dates of refills are usually recorded in the pharmacy database. The Medication Possession Ratio (MPR, objective measure) is a method for calculating adherence rate from refill data with the following formula: days' supply divided by the days of the interval of interest.

Purpose of the Study

We aimed at assessing whether the affirmative answer to the PMC question "Do you sometimes forget to take your medication?" coincides with a Medication Possession Ratio (MPR) <90% (non-adherence) in DOAC treated patients.

Method

Fifth-year pharmacy students recorded one PMC with an anticoagulated patient during internship in community pharmacies between November 2014 and March 2015. Patient's refills of the past 12 months were used to calculate a MPR if at least two refills were available. Assumptions for the calculation of the MPR were taken from literature [288].

Results

The 69 PMCs concerned DOACs for 30 (43.5%) patients (52% women, 73.0 ± 12.2 years old, 9.9 ± 4.9 medications). The most often prescribed DOAC was rivaroxaban (93.3%), apixaban and dabigatran were marginally prescribed (3.3% each). Five cases were excluded due to less than two refills. All 25 remaining patients were treated with rivaroxaban.

Refills (mean of 2.9±0.8 per patient) were available for a mean of 128±62 days. MPR ranged from 50.2 - 182.7%. MPR below 90% was observed in 4 patients (16%) (Figure 1), out of them two self-reported to sometimes forget to take the DOAC. Other two patients reported non-adherence but showed a MPR >90%. Oversupply up to 110% was observed for 7 patients, and excessive oversupply for 6 patients (MPR: 114-183%).

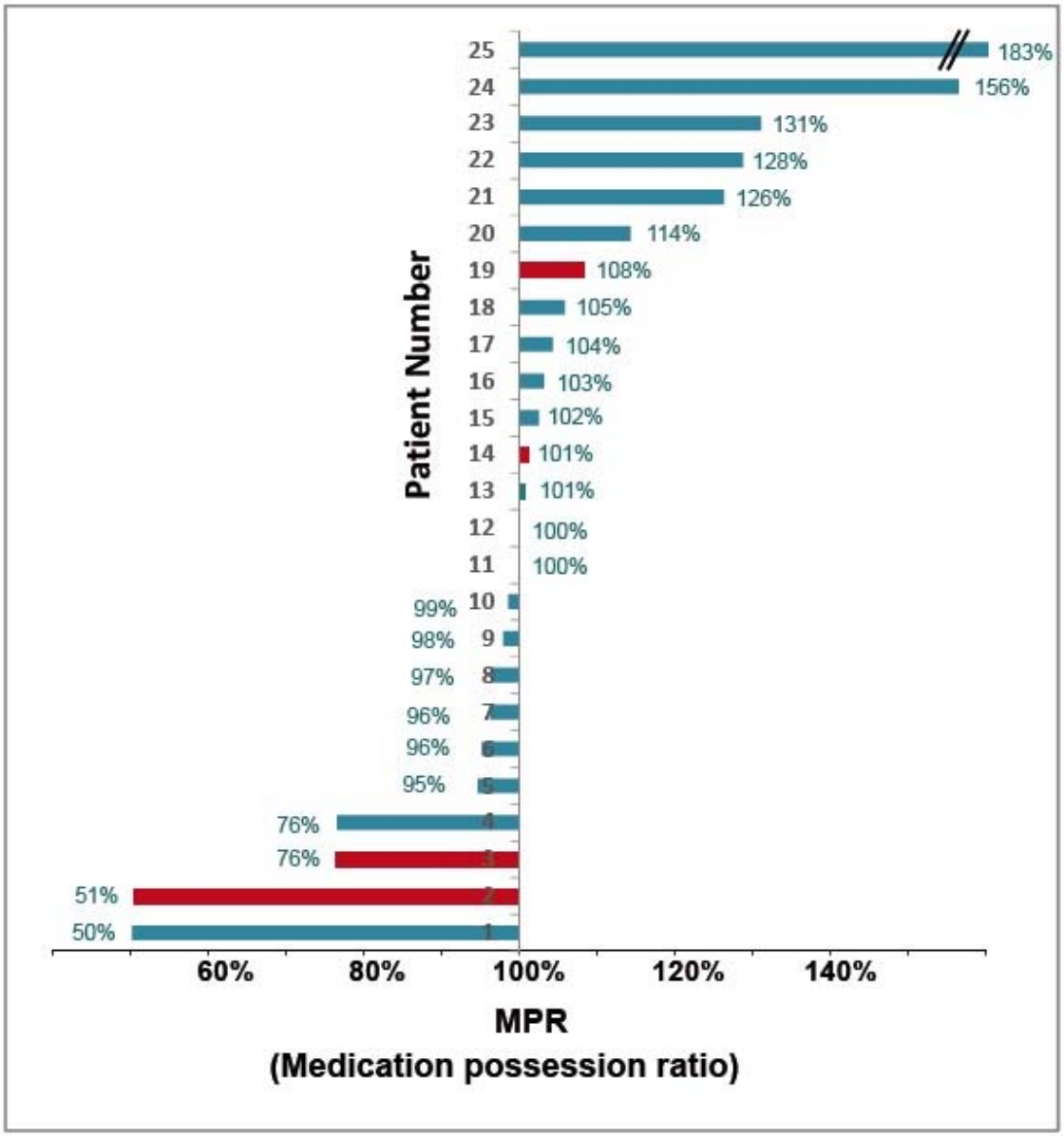


Figure 1: MPR of 25 included patients. MPR bars of patients who self-reported non-adherence are indicated in red.

Conclusion

Objective and subjective measures of non-adherence coincided poorly. One reason might be that the expression «Forget sometimes» might not mean skipping a dose and thus, might not translate into a reduced MPR value. To «Forget sometimes» may be interpreted as a simple delayed intake. We question the wording of the question that might be equivocal, and further the appropriateness of objective measures such as the MPR as single trigger to adherence counselling. Composite adherence measures may help to establish a more precise picture of adherence. In future, pharmacists should screen for non-adherence by combining MPR and for example a medication review.

9 Project D: Study proposal in anticoagulation

9.1 Impact of a tailored and stepwise educational program on adherence to rivaroxaban therapy in Switzerland – adaptable to other European countries such as Germany or France [D]

Study proposal, unpublished

Impact of a tailored and stepwise educational program on adherence to rivaroxaban therapy in Switzerland

– adaptable to other European countries such as Germany or France

1. Project description

Scientific domain: Pharmaceutical Care / Anticoagulation therapy

Key words: rivaroxaban, community pharmacies, educational program, adherence monitoring, pharmaceutical care

Ethics committee approval: required

2. Administrative information

Coordinating center: Basel

Project sites: community pharmacies and cardiologists in the region of Basel, Switzerland

Duration of project: 9 months

3. Abstract

Published evidence suggests that non-adherence to anticoagulation in general and to rivaroxaban in particular is common. Previous work by our group showed that electronic monitoring of adherence to polypharmacy along with feedbacks allows improving intake patterns. A community 2-arm project is proposed where patients with a first prescription of rivaroxaban are allocated to A) usual care in control community pharmacies, B) educational intervention in trained pharmacies. Randomization will occur at pharmacy level. All community pharmacies located in the North-West German-speaking part of Switzerland (Basel Stadt and Land, Aargau, Solothurn; approx. 300) will be invited to participate and to recruit patients. In parallel, cardiologists will recruit patients, suggest the participation in an educational project and direct them to a pharmacy of their choice (interventions and control).

Eligible will be patients aged 18 or older with a first prescription of rivaroxaban for atrial fibrillation. Patients accepting to participate (gave Informed Consent) will obtain A) either rivaroxaban in original packages equipped with smart recorder cards (4DD® cards) or B) their oral medicines in smart weekly dispensers (in Switzerland: Pharmis® punch cards equipped with electronic wires POEMS; in other European countries: currently used weekly pillbox equipped with smart recorder cards). Patients will be asked to bring back used packages (original and repackaged) for downloading data. The project duration will be 9 months. The educational program (intervention) will focus on knowledge and adherence of the entire medicine schedule (polypharmacy). Patients will be proposed several educational units according to their current needs and problems (tailored and stepwise), followed by 3 months with intensified pharmaceutical care including additional feedback on their electronically monitored intake pattern. Outcomes to be monitored include: adherence (self-reported, taking, timing, clusters), drug-related problems, quality of life, and satisfaction. Data collection points comprise baseline (T_{first}), and at every smart refill (every 2-4 weeks for the whole project duration of 9 months (T_{last}).

The intervention starts with the patients' screening questionnaire and the educational program for patients. Community pharmacists providing the interventions will be trained on how to provide feedback with individual electronic adherence data. Continuing coaching will be provided. Data analysis will be divided into intervention pharmacies and control pharmacies. Between-group (bivariate) and multivariate analysis will enable to identify factors that may explain different levels of success of the educational intervention and of the intensified pharmaceutical care on patients outcomes. For all tests, a confidence interval of 95% will be considered.

4. Abbreviations

ACTS	Anti-Clot Treatment Satisfaction questionnaire
AF	Atrial fibrillation
A14	Adherence scale 14
DVT	Deep vein thrombosis
DOAC	New oral anticoagulants
OAC	Oral anticoagulants
PE	Pulmonary embolism
PMC	Polymedication check
POEMS	Polypharmacy electronic monitoring system
SF-12	Short form 12
S-TOFHLA	Test of functional health literacy in adults
VKA	Vitamin K antagonists

5. Background

5.1 Atrial fibrillation

Atrial fibrillation (AF) is the most common form of sustained arrhythmia. The prevalence of AF in the general population is 1% and estimates suggest its prevalence is increasing [289, 290]. AF is commonly associated with other diseases such as hypertension, heart failure, heart disease and diabetes. If AF is left untreated, patients are on significant risk for stroke and other morbidities. The aim of treatment is to prevent complications, particularly stroke, and to reduce symptoms. Drug treatments include anticoagulants to reduce the risk of stroke and antiarrhythmic drugs to restore or maintain the normal heart rhythm or to slow the heart rate in people who remain in AF. In June 2014, the National Institute for Health and Care Excellence (NICE) - guidelines for the management of AF have been revised and introduced major changes to stroke risk assessment in patients. Assessment of CHA2 DS2-VASc risk should be undertaken for all patients with paroxysmal, persistent or permanent AF, those with atrial flutter and those who have converted back to sinus rhythm but are at risk of arrhythmia recurrence. Oral anticoagulation should be considered in men with a CHA2DS2-VASc score of 1 and offered in all patients with a CHA2DS2-VASc score of 2 or above, taking bleeding risk into account [291]. Thus, rate for oral anticoagulation use will increase in the next years.

5.2 Oral anticoagulation therapy

After 30 years of vitamin K antagonists (VKA) use, new oral anticoagulants were developed and become more popular. Rivaroxaban, a direct factor Xa inhibitor, is approved and indicated in the treatment of deep vein thrombosis (DVT), pulmonary embolism (PE) and the prophylaxis of DVT after hip or knee replacement surgery, the prophylaxis of stroke and systemic embolism in non-valvular atrial fibrillation (AF), and after acute coronary syndromes. Maintaining appropriate anticoagulation with VKA is challenging. Therefore switching patients with poor control to rivaroxaban may improve therapeutic outcome due to rivaroxaban's favorable pharmacokinetics. Additionally, doses do not change and no monitoring is necessary making treatment with rivaroxaban more convenient for patients than therapy with VKA. On one hand, rivaroxaban therapy has relevant advantages for patients. On the other hand, rivaroxaban has a short half-life and therefore an increased risk of thrombosis after the omission of one dose [145]. Thus, the once daily intake regimen requires a strict timing adherence to ensure appropriate therapeutic coverage. Finally, consultations for controlling blood values in patients taking VKA will not be necessary anymore, and the opportunity to discuss aspects of adherence during such encounters will not be possible.

5.3 Adherence to oral anticoagulants

Adherence is defined as “the extent to which a person's behavior - taking medicine, following a diet, and/or executing lifestyle changes - corresponds with agreed recommendations from a health care provider” [1]. The level of adherence to medicine varies greatly and is related to treatment, patient, and /or health care provider [2]. Intentional non-adherence reflects the active decision of the patient not to take his medicine as prescribed. This is a rational process where patients beliefs and concerns are important factors influencing the motivation to take the medicine. Unintentional non-adherence can be considered as an accidental process. The patient does not take the medicine as prescribed due to forgetfulness or not knowing how to use his medicines or other barriers.

Non-adherence in patients with AF or in patients treated with OAC for other reasons is a common problem. Non-adherence rates were observed in up to 32 % patients treated with warfarin [146] and only 52% of patients with AF are adherent to a once daily drug regimen 18 months after treatment initiation. [292] Data from patients maintained on short-term thromboprophylaxis with rivaroxaban suggest low non-adherence rates (4%) but these patients are at a considerably increased risk for complications(e.g. pulmonary embolism) [293]. In general, medicine adherence for patients treated with new oral anticoagulation for chronic conditions has been poorly documented. Rodriguez et al., stated that rates of premature discontinuation with DOACs in registration trials range from 2.3-37%, in which 11% (range 3-14.3%) no apparent reason for discontinuation is available [147]. A recent project observed adherence rates, given as proportion of days covered, of 0.86 (SD: 0.19) in patients treated with rivaroxaban [294].

5.4 Interventions to enhance adherence to oral anticoagulants

Simplifying treatment regimen for anticoagulation and other conditions may improve medicine adherence, which can potentially prevent therapy failure and adverse events. The addition of a reminder system was shown to increase adherence (pill counts) by 4.1 – 4.3% in HIV patients [295] and reminder systems combined with dose simplification were shown to decrease rate of non-adherence by 24-26% [147]. A recent Cochrane review [44] found that current methods of improving medicine adherence for general chronic diseases are mostly complex and not effective. Another review showed that patient education about disease and medicine knowledge is not sufficient for addressing non-adherence while self- efficacy is an important factor [50]. Controversially, two studies showed that enhancement of patient knowledge about OACs and the underlying disease were associated with improve long-term adherence or better therapeutic outcome [81, 82]. Another review on patient education and OAC therapy [61] stated that the process of patient

education is influenced by literacy/language barriers, cost-effectiveness of the programs, and accountability in educational outcomes. Therefore, improving anticoagulation outcomes needs first the prioritization of the educational content for the development of meaningful long-term interventions. Additionally, there is a need for validated instruments measuring outcomes after patient education, for objective adherence measures and for sufficient project power enabling the detection of improvements in adherence and clinical outcomes. Because usually the OAC therapy represents just one element of a medicine regimen, polypharmacy needs to be considered. One can assume that DOACs - in contrast to VKAs - are perceived as ordinary oral medicine due to the absence of specific monitoring and dose adjustment. Therefore, adherence interventions need to consider the patient‘s current polypharmacy. Unlike a currently performed project on education program for Eliquis® (AEGEAN, ClinicalTrials.gov: NCT01884350), we will address all medicine in the educational program and measure adherence to all medicine.

5.5 Pharmacy-led counseling in Switzerland

5.5.1 Polymedikation check (PMC)

Since 2010, community pharmacists in Switzerland can offer a medicine use review, the so called Polymedikation check (PMC), to patients on ≥ 4 prescribed drugs taken over ≥ 3 months. The PMC is based on the Medicines Use Review (MUR) from the United Kingdom [41]. This type of pharmacist-led medicine review services are available in several other countries such as the United States of America, Australia, Canada, and New Zealand [37-40]. The PMC focuses on drug-related problems, adherence issues, and the need for suppling of the medicine in a weekly pill organizer. This service is well implemented in Switzerland and remunerated as a cognitive service (Annex A). A recent evaluation of the PMC showed a consistent trend for improved adherence rates in patients treated with antiaggregation drugs after receiving a PMC, however without reaching significant level [296].

5.5.2 Weekly pill organizer

A recent project showed that during a PMC in patients treated with OAC, pharmacist offered in 72.5% of the cases the use of a dose dispensing aid such as a weekly pill organizer. Dose dispensing aids (e.g. Dosett®, Pharmis®) are frequently supplied to older patients with complex medicine use in Switzerland and Australia and other European countries such as Holland, Spain, France and the UK [297]. In Switzerland, the delivery of a weekly pill organizer is reimbursed by the health care system. In its function as drug reminder systems, dose dispensing aids allow to improve non-intentional non-adherence. The impact of these drug reminder systems has been

evaluated in a systematic review: positive effects on adherence and clinical outcomes were clearly demonstrated [298].

5.6 Adherence assessment methods

Adherence can be measured directly or indirectly. The quality of different adherence measurements was assessed in a recent review [20]. In brief, the authors concluded that composite measures are important to establish a detailed picture of adherence. From all available indirect adherence assessment methods, the electronic monitoring represents the most objective measure and is recommended as the method of choice in research on adherence [30]. Up to now, electronic monitoring of one medicine was feasible using devices such as the MEMS® caps (Medicine Event Monitoring System). In several studies using these electronic caps, discussing the adherence profiles with the patients had a significant impact on patient outcome, mainly through a shared decision of the follow-up strategy [32]. However, only one single medicine was monitored and the derived intervention focused on that specific medicine.

Recently, our group developed a monitoring system for polypharmacy named **POEMS** (Polypharmacy Electronic Monitoring System; see Figure 1) [33]. It consists of a paper foil with imprinted electronic components that measure the electrical resistance and record the time of its changes when a loop is broken, i.e. when a cavity is emptied. The patient's entire oral solid medicine is filled in a disposable multidrug punch card with 7x4 cavities (Figure 1), equipped with the foil on its backside [33]. In a previous project [299], we combined biomarker measurements with this new method of electronic adherence monitoring of solid oral drugs. The use of POEMS allowed to rule out non-adherence and therefore to assess drug-drug interactions, whereas pharmacogenetic tests and biomarker assessments allowed the identification of contributing factors when the lack of biomarker response persisted.

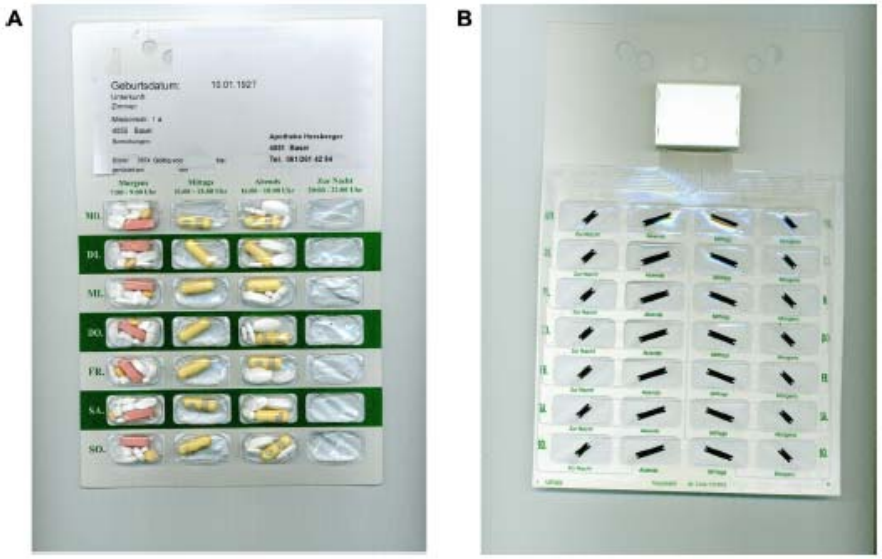


Figure 1: A) Front side of a commercially available multidose punch card (Pharmis GmBH, Beinwil am See, Switzerland) with 4 x 7 cavities pre-filled with a patient's individualized medication regimen. B) Rear side covered with an electronic film of conductive tracks, a battery and an antenna, and a microchip housing (ConferenceClinique S.A. Lausanne, Switzerland).

The **recorder card 4DD®** was developed by the company Adherence innovations (based in The Netherlands; www.adherence-innovations.com) to help patients remember the intake of medicines through an alarm flashing (light) and beeping (sound; see Figure 2). With a clip system, the card can be affixed to original packages or weekly pill organizers. The development of a smart version will enable to obtain electronic monitoring data. Patients will press the red button at the time of the intake, and register the intake event with exact date and time. For both systems (POEMS and 4DD® card), the data are transferred to a web-based database, either via a wireless communication device (NFC for POEMS) or a plug cable (USB for 4DD® card).

Figure 2: Reminder card 4DD® (Adherence innovations, The Netherlands). Up to four intake times can be programmed either by the pharmacist or the patient himself. Pressing the red button will register the intake with date and time.

6. Plan and methods

6.1 Overall goals

A) To develop a stepwise educational program on anticoagulation in general and on rivaroxaban in particular and to evaluate its impact in ambulatory patients under polypharmacy. The research question is: *"Can a pharmacy-based educational program contribute to ameliorate the adherence to first-time rivaroxaban in ambulatory patients under polypharmacy?"* The educational program should be easy to implement in daily practice.

B) To develop a stepwise educational program on adherence using feedback from electronic monitoring. The research question is: *"Can a pharmacy-based educational program followed by individualized feedback from electronic monitoring (= intensified pharmaceutical care) contribute to enhance timing-adherence to rivaroxaban in ambulatory patients under polypharmacy?"*

6.2 Specific aims

The aims are a) to investigate the impact of the intervention on subjective (questionnaire based) and objective (electronically monitored) adherence; b) to assess patient satisfaction with an educational tailored and stepwise program on anticoagulation therapy.

6.3 Project hypothesis

I. Patients in the educational intervention group will have higher taking adherence than patients in the control group.
II. Patients in the intervention group will have a better knowledge of anticoagulation and rivaroxaban at the end of the project (after 9 months) than patients in the control group.
III. Patients in the intervention group will declare satisfaction with the educational program, independently of the electronic monitoring system.
IV. Patients in the intensified intervention group will have higher timing adherence after additional feedback on intake pattern at the end of the project (V10, after 9 months) compared to V8 (after 7 months).

6.4 Project design

This is a prospective project with 2 groups, with cluster randomization at the pharmacy level (intervention pharmacy or control pharmacy; Figure 3). Patients fulfilling all inclusion criteria and no exclusion criteria will be served by one of the two pharmacies:

1A) Intervention pharmacy (I-Apo) for Switzerland: All oral medicines will be dispensed in Pharmis® multidrug punch cards equipped with the electronic monitoring system POEMS, medicines will be reviewed (PMC), at least 2 educational sessions will be dispensed, after 7 months (V8) additional individualized feedback based on the individual intake profile will be provided.

1B) Intervention pharmacy (I-Apo) for other European countries: All oral medicines will be dispensed in locally available multicompartment weekly organizers (e.g. www.medi-7.de) equipped with the smart recorder cards, medicines will be reviewed (according to locally current practice), at least 2 educational sessions will be dispensed, after 7 months (V8) additional individualized feedback based on the individual intake profile will be provided.

2) Control pharmacy (C-Apo): Rivaroxaban original package will be equipped with smart recorder cards, medicines will be reviewed (in Switzerland: with PMC; in other European countries: according to locally current practice), routine care will be dispensed, no specific education and no feedback to individual intake profile.

6.5 Interventions

There will be two types of interventions provided by the intervention pharmacies (1) the educational program and (2) the intensified pharmaceutical care program with feedback. Both need to be developed and tested. The following elements represent key elements of the interventions:

The educational program consists of (a) one main session at the first contact, (b) one consolidation session at the second contact, and (c, d, e) further 3-7 deepening sessions at the remaining contacts until V7. The main session will start with a medicines review (PMC). A questionnaire will allow detecting further individual patient needs (beliefs and concerns, perceived barriers, motivation, environment, and competencies).

The intensified pharmaceutical care program starts after 7 months and will be provided only at sessions V8-V10. It consists of visualizing the past intake pattern obtained with the electronic monitoring, providing feedback based on the individual patient profile and stressing the need of time adherence, or adapting the treatment plan in collaboration with the physician. Reasons for delayed and/or premature intakes will be investigated, and according practical solutions will be proposed.

6.6 Recruiting centers

Community pharmacies accepting to participate (see Tasks 7.5) and dedicated cardiologists in the region of Basel, Switzerland. The intervention will solely be provided in the community pharmacies.

6.7 Population and sample

Inclusion criteria:

- patients with AF newly prescribed rivaroxaban
- taking at least 2 additional oral solid drugs
- aged 18 years or older
- self-managing their medicine
- capable to give informed consent in German language

Exclusion criteria:

- patients with a diagnosis of declared dementia
- patients who are supported in their drug management through a home care organization
- patients using a weekly medicine aid system (control and educational group; daily medicine aid is not an exclusion criteria)

Sample:

To detect an expected absolute difference (effect size) of 11% between the taking adherence rates of the control group (76% according to Di Matteo 2004 in cardiovascular diseases [5]) and the educational intervention group (87%; 20% absolute difference (effect size) would be possible according to Lee 2006 in combination with a reminder system after 6 months of intervention [300]), we need a sample size of 67 patients per group and a minimum of 20 recruiting pharmacies per group, based on the assumptions that participating pharmacies will recruit a mean of 7 patients [296] and of a fairly small clustering effect of 0.05 (0.026 would be possible according to Sturt J.A. in a cluster randomized trial on diabetes education in primary care [301]).

- with a level of significance set at 5% (one-sided)
- with a power of the project set at 80%
- with a standard deviation in the population set at 30% and 20%, for the control and the educational intervention group, respectively

An additional sample of 50 patients and 15 recruiting pharmacies (educational group) is needed to detect an expected absolute difference (effect size) of additional 10% between the taking adherence rates of the educational (87%) and the adherence enhancing program (97%) after 9 months of project duration, based on the assumption that participating pharmacies will recruit a mean of 7 patients and a fairly small clustering effect of 0.05.

- with a level of significance set at 5% (one-sided)
- with a power of the project set at 80%
- with a standard deviation in the population set at 20% in both groups (educational and educational plus intervention)

(calculated with http://sampsize.sourceforge.net/iface/s2.html#means).

In total, we need a sample of 216 patients with an anticipated drop-out rate of 32 patients (17%) [296]. Cardiologists will recruit patients, suggest the use of electronic punch cards to manage medicine, and direct patients to the pharmacy of their choice (interventions and control). In parallel, project pharmacies will be instructed to recruit patients. The project will be terminated when 216 patients will be recruited. Randomization will occur at the pharmacy level. The project duration will be 9 months after inclusion.

Follow-up: Patients who want to continue obtaining their polypharmacy in punch cards after completion of the project will be served accordingly by the community pharmacy but the electronic monitoring will be removed.

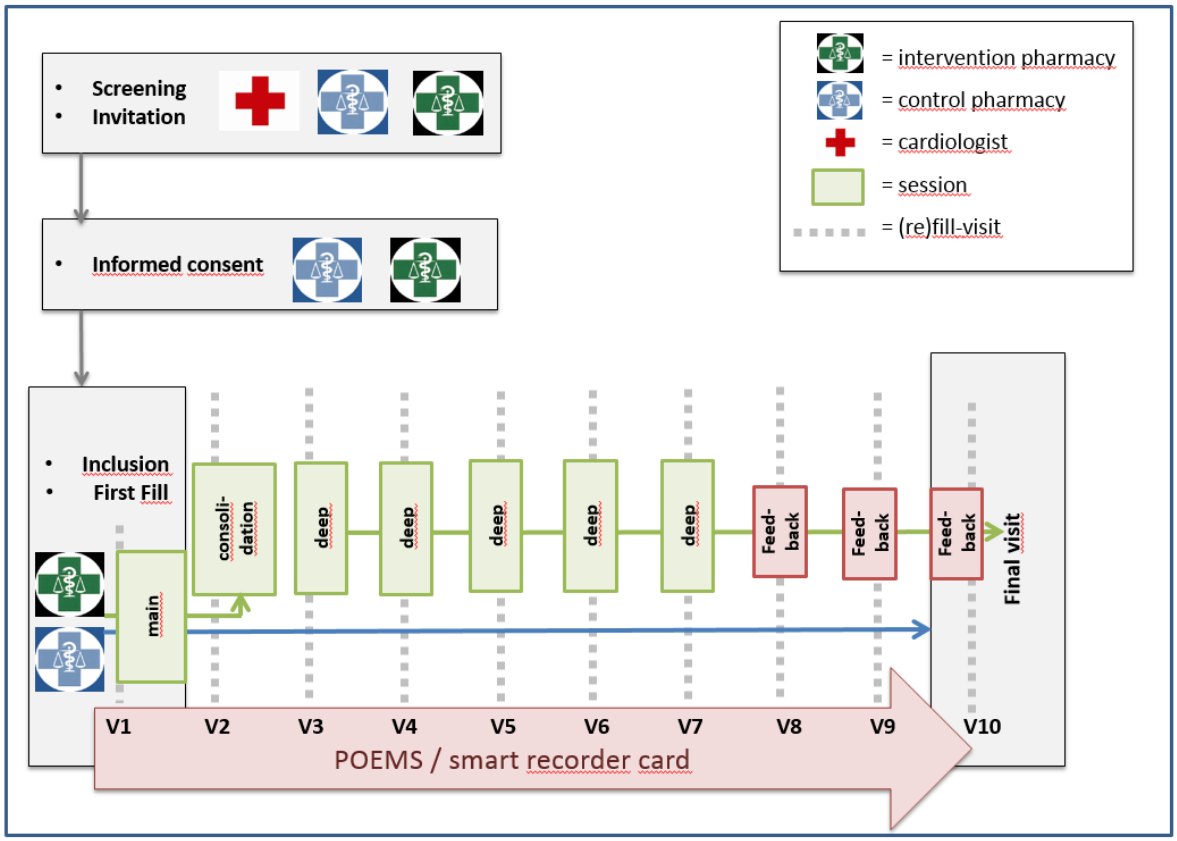


Figure 3: Project flow chart.

6.8 Drug-related problems

Given the type of intervention, we cannot think of any adverse events that will be directly related to the trial. We will ask pharmacists to record drug-related problems with a specific classification tool [302]. We will develop an open questionnaire where patients will be invited to name any drug-related problem in daily life they may have experienced from the intervention.

6.9 Informed consent

Patients participating in this trial will all have to provide written informed consent for participation in the trial.

6.10 Method of masking

This is an open intervention project. Pharmacists and patients will not be blinded to the intervention. Patients in the educational intervention group and in the control group will not be blinded to the compliance monitoring (POEMS or smart recorder card). Patients will be instructed to bring their

rivaroxaban original package every month back for downloading data. Responsible clinicians will be informed monthly about pharmacist-led interventions and at the end of the project about results from the electronic monitoring.

6.11 Process measures

An overview of data which will be assessed is given in Table 1.

I. Subjective non-adherence will be assessed using the A14 adherence questionnaire [303] in its German version. This is a 14-item questionnaire with 5-point Likert scale ranging from "never" (4 points) to "very often" (0 point). It takes about 7 minutes to complete. Patients with a total score of 50-56 points are classified as "adherent", those with a lower score as "non-adherent". We obtained the right to use the questionnaire.

II. Objective non-adherence will be assessed electronically (with POEMS and smart recorder card in Switzerland; with smart recorder card in other European countries).

III. Health Literacy will be assessed using the short version of the Test of Functional Health Literacy in Adults (S-TOFHLA) [304]. Health literacy represents the cognitive and social skills of individuals and determines the motivation and ability to gain access to, understand, and use information in ways which promote and maintain good health. Health Literacy means more than being able to read information and successfully make appointments and additionally addresses the environmental, political, and social factors that determine health [50]. The S-TOFHLA contains 4 numeracy tests and 2 prose passages and takes a maximum of 12 minutes for answering. The S-TOFHLA is a practical measure and can be used to identify individuals who require special assistance to achieve learning goals. It has been translated into German and was shown to be reliable and valid. [305]

IV. Patient satisfaction with anticoagulation therapy will be assessed with the Anti-Clot Treatment Satisfaction questionnaire (ACTS), a specific treatment satisfaction questionnaire. This 15-item self-report questionnaire includes 3 questions concerning benefits and 12 questions concerning burden of anticoagulation therapy. Patients will be asked to report their experience with anticoagulant treatment during the last 4 weeks on a 5-point Likert scale (1= not at all, 2= a little, 3= moderately, 4 quite a bit, 5= extremely). The ACTS has been translated into German. The ACTS burdens and ACTS benefits scales consistently satisfied traditional reliability and validity criteria, confirming its clinical

usefulness as a self-reported instrument of patient satisfaction with anticoagulant treatment in clinical trials. [306]

V. Quality of life will be assessed using the SF-12, a short version of the SF-36. This self-report questionnaire measures functional health and well-being with 12 items from the patient's point of view. It is a practical, reliable and valid measure of physical and mental health that can be completed in five to ten minutes [307]. The SF-12 has been translated into German and validated in patients with coronary heart disease. The summary measures replicate well the SF-36 summary measures and showed similar responsiveness to change. [308]

VI. Knowledge on anticoagulation, rivaroxaban.

VII. Needs of patients (screening tool for the intervention group) and patient reports in the control group.

VIII. Drug related problems and corresponding interventions will be assessed with the classification system “pharmDISC” during the medicine review PMC and at each refill visit the intervention groups (education and education-plus groups). This system was developed and validated by our research group for the classification of drug-related problems and pharmaceutical interventionsin community pharmacies [302].

Table 1: Overview of data collection (I-Apo = Intervention pharmacy; C-Apo = control pharmacy); (X) = facultative, according to local practice

	Patient characteristics, Health literacy (S-TOFHLA)		**Drug related problems Patient needs**		**Patient knowledge**		**Satisfaction (ACTS), Quality of life (SF-12), Subjective adherence (A14)**		**Objective adherence (POEMS, smart card recorder)**	
	I-Apo	C-Apo	I-Apo	C-Apo	I-Apo	C-Apo	I-Apo	C-Apo	I-Apo	C-Apo
V1	X	X	X	X	X	X	X	X		
V2			X	(X)	X	X	X	X	X	X
V3			X	(X)					X	X
V4			X	(X)					X	X
V5			X	(X)					X	X
V6			X	(X)					X	X
V7			X	(X)					X	X
V8			X	(X)	X	X	X	X	X	X
V9			X	(X)					X	X
V10	X	X	X	X	X	X	X	X	X	X

6.12 Outcomes

Adherence:

- subjective: self-report using A14 at baseline (V1), at V2, V8 and at last visit for all groups.

- objective: values obtained from electronic intake data:

Taking adherence $= \%\ of\ doses\ taken\ = \frac{number\ of\ events}{number\ of\ prescribed\ doses}$

Timing adherence $= \%\ of\ doses\ taken\ within\ a\ specific\ grace\ interval$

$= \frac{number\ of\ events\ within\ a\ specific\ grace\ interval}{number\ of\ prescribed\ doses}$

Time variability in drug intake $\frac{\sum_k |t_{ik} - median(i)|}{Number\ of\ prescribed\ dosing\ days\ for\ subject\ i}$

Days without dosing = $\frac{Number\ of\ days\ without\ events}{Number\ of\ prescribed\ dosing\ days}$

Percentage of too short (overdosing) or too long (underdosing) intervals

Clustering methods will be used to identify pattern of adherence and different clusters will be compared to a variety of patient characteristics. [309]

Health literacy will be assessed at baseline (V1) and last visit (V10) for all groups.

Patient satisfaction with anticoagulation treatment will be assessed at baseline (V1), V2, V8 and at the final visit for all groups.

Knowledge of anticoagulation and treatment will be assessed at baseline (V1), V2, V8 and last visit for all groups.

6.13 Analysis

Bivariate analysis will include a) between-group analyses (Chi-squared test for categorical variables, Students t-test or Mann-Whitney test for continuous variables). These analyses will be performed at baseline and at the end of the project to evaluate the impact of the interventions. The effect over time b) will be assessed using within-group analyses of the intervention group (Wilcoxon test for continuous variables in several time points). Multivariate analysis will include c) factor analysis to detect factors associated with successful interventions.

6.14 Data generation, data entry, blinding

Patient data will be generated at the community pharmacies and entered into their local software as part of their routine. A checklist will describe the content of each visit. Thus, it will guide pharmacists through each visit. All data from the questionnaires will be sent together with the CRF to the clinical project center by post mail or e-mail. Electronic monitoring data from the POEMS will be sent electronically by the pharmacist during medicine refill to the server of the pharmacy project center. The pharmacy project center will be responsible for coordinating, checking, and exporting of all electronic data from the POEMS / smart recorder card for reports to physicians.

7. Tasks

7.1 Development of tools and their scores

7.1.1. Main educational session (V1)

This session will deal with **basic information** on AF, anticoagulation in general, and therapy with rivaroxaban in particular. All educational topics according to the review of Wofford et al, appropriate for rivaroxaban therapy will be included [61]. As much information and material (booklets) as possible will be taken from the European Heart Rhythm Association (EHRA) practical guide [310]. Complementary information about the co-medicine will be given (purpose, expected effects). All given information will agree with the Swiss Summaries of Product Characteristics [133]. Self-management with punch cards will be explained and electronic monitoring will be disclosed.

7.1.2. Consolidation session (V2)

This session will check which information the patient could retain from the basic information dispensed at the first session. Elements missing for whatever reason will be repeated. Individual patient needs will be checked and prioritized. Current problems with medicine management (e.g. side effects, persistence with treatment) will be assessed. Solutions will be proposed and shared decision of the follow-up strategy will be made.

7.1.3. Deepening educational sessions (V3-V8)

They will focus on individual needs for deepened knowledge and recurrent problems will be assessed. Solutions will be proposed and shared decision of the follow-up strategy will be made.

7.1.4. Screening for needs at first visit (V1)

Evidence on barriers and facilitators were taken from the literature and compiled in a self-administered questionnaire.

7.1.5. Knowledge Questionnaire (V1, V2, V8, V10)

Existing questions from the literature were compiled and evaluated by an expert panel. The final self-administered questionnaire contains 15 questions and will be tested for readability, acceptability and comprehension in a convenience sample. It will be validated in a sample of approx. 30 patients and 30 pharmacists for criteria defined by Fitzpatrick [311].

7.1.6. Pilot testing of the screening tool

The tool for the screening of patient needs will be pilot tested in a convenience sample for acceptability, comprehension and readability.

7.2 Request of existing tools

Existing validated tools in German (S-TOFHLA, ACTS and SF-12) will be requested from their owners.

7.3 Case report form (CRF)

CRFs for intervention and control pharmacies and for recruiting cardiologists will be developed. They will contain the responses of the patients to the questionnaires, baseline data, notes and minutes, and adherence data.

Data collected through electronic system will be accessible through pseudonymization (i.e. keeping patients privacy and date confidentiality but allowing access for authorized persons). Data collected on paper sheets will be anonymized with patient identification codes.

7.4 Ethic committee approval

The project will be submitted to the Ethical Committee Nordwest Schweiz for approval.

7.5 Recruitment of the pharmacies

For the recruitment of educational plus intervention pharmacies addresses of the community pharmacies offering punch cards in the North-West German- speaking part of Switzerland (Basel- Stadt and Land, Aargau, Solothurn) will be provided by Pharmis AG. This company is the leading provider of software and support for repacking medicines into blister punch cards (www.pharmis.ch). For the recruitment of educational and control pharmacies all community pharmacies of the cantons Basel Stadt and Basel Land pharmacies will be invited to participate by an invitation letter.

7.6 Recruitment of cardiologists

Contact has been made with several cardiologists and the discussion about their participation is ongoing.

7.7 Education of pharmacists

Previous research from our group has identified that the training of pharmacists in view of performing a clinical project is best conducted in 2 steps.

During an initial meeting at the university general information on the project will be given to the participating pharmacists. Medication knowledge will be updated giving information about rivaroxaban / AF treatment including handouts (DOAC leaflet by Bayer®, EHRA guide).

The different aspects and the importance of adherence will be pointed out and tools (questionnaires, screening tool, and documentation of interventions) and data collection will be introduced. Stepwise patient education as described above will be shown. Teaching adherence measurement methods like electronic data monitoring (POEMS) will also be part of the education program. Possible difficulties should be uncovered and solved. A training video with a pseudo-patient will be produced to show important steps of the interventions and handling of the CRF, the video will be online available during the study.
The second meeting will take place at the community pharmacies. During a visit, a researcher will run a fictitious case to check all elements (questionnaires, data gathering tools, and web application). The correct application of data gathering tools is essential for this project.

7.8 Coaching of the pharmacists

All training elements (power points slides, training videos, documents, and checklists) will be available online on PCRG website (www.pharmacare.unibas.ch). Experience from a previous project in our group showed that project pharmacists are repeatedly viewing online information intended for them. A hotline will be implemented to help pharmacists e.g., when they encounter a problem while they are in contact with a patient. Other information will be delivered via phone call or video conference (skype).

7.9 Electronic monitoring

POEMS technology and smart recorder cards will be disseminated to the project pharmacies (POEMS films, electronic devices, data reader, and login for the web application). Pharmacists will be able to allocate an electronic punch card or smart recorder cards to a specific patient, to read the returned punch card, and to visualize the intake pattern with the patient. They will not have access to the database. The responsible investigator will have administrator access to the entire database.

8. Significance of the planned work

We see several impacts of the planned work on national and international levels.

First **in Switzerland**, our results may contribute to implement a specialized cognitive service in addition to the generic Polymedikation Check. It could be added to the "Leistungs Orientierte Abgabe (LOA)" contract between community pharmacy and health care insurance. The new "educational anticoagulation service" will provide support for patients with a new prescription of rivaroxaban for long-term conditions and will ensure safe medicine use and improve medicine adherence.

Second on **international level** where medicines review services are already known (UK, NL, United States of America, Australia, Canada, and New Zealand [37-41]), the extension of the medicines review with an educational anticoagulation part could be realized. In countries without medicines review services, the educational anticoagulation service could be proposed to the local health care system.

Third, our results may help stakeholders to evaluate the benefits of electronic drug reminder packaging. The use of such reminder blisters is increasing, equally in countries without reimbursement such as Germany [312]. Our results could serve local health care systems.

Finally, our results may support the positive impact of education and knowledge on adherence in general, and on adherence to rivaroxaban in particular.

10 General discussion and conclusions

This thesis contributes to a better understanding of patient knowledge and preferences. The goal was to assess patient knowledge of anticoagulation, patient preferences for VB12 therapy, and to develop an educational program on adherence for outpatients with rivaroxaban therapy (adaptable to all DOACs). Further, assessment instruments for knowledge, preferences and adherence in German were created. Because underlying concepts are complex, this goal was approached in four distinct projects. Consequently, in this thesis various methodologies were applied such as focus group discussions, semi-structured interviews, evaluation of biomarker levels, applied observational studies as well as randomized parallel group designs.

Patient knowledge about oral anticoagulation therapy

Project A consisted of two studies. First, we aimed at screening for knowledge gaps about OAC in outpatients treated with VKAs or DOACs. We therefore amended the basic PMC with specific questions on OAC and assessed its impact on knowledge in an observational study (**Study A-1**). Because no specific DOAC knowledge assessment questionnaire was psychometrically validated and published, we developed and validated a questionnaire to self-assess knowledge about DOAC (**Study A-2**). The KODOA-test can be used in clinical trials to determine associations between knowledge of DOAC and adherence or clinical outcomes.

Screening for knowledge gaps about OAC in outpatients was achieved with the basic PMC which was amended with specific questions about OAC. These questions were derived from a French publication about the evaluation of a pharmaceutical interview in an anticoagulation clinic [151]. Questions were translated into German, formulated as open-ended questions and placed at the very end of a basic PMC in form of a semi-structured interview. In the observational study **A-1,** patients on VKAs or DOACs received the amended PMC. The study demonstrated that the majority of patients had knowledge gaps concerning OAC and that half of the patients did not know how to proceed in case of a missed dose. Our findings are in agreement with other studies that observed that a majority of patients treated with OAC had poor or inadequate knowledge of the treatment [152-154]. We further found a trend that patients with DOAC therapy were more likely to have knowledge gaps compared to patients on VKAs. A recent survey of the European Heart Rhythm Association (EHRA) showed also that there is room for improvement regarding education of patients taking OACs [313]. A lack of knowledge of OAC sets patients at risk for medication errors, induces low self-care behavior and causes poor health outcomes [49]. We

observed high prevalence of knowledge gaps regarding OAC therapy, predominately in patients on DOAC. This observation served as a rationale for further projects on knowledge about DOAC. In particular the development and validation of a specific questionnaire to self-assess knowledge of DOACs in clinical trials and the development of a study protocol for a cluster-randomized controlled trial that investigates associations between enhanced DOAC knowledge and improved adherence (**Studies A-2** and **D**).

We further observed that identification of knowledge gaps led pharmacists to provide educational counselling spontaneously. Although unstructured, the provision of this targeted and tailored counselling increased patients' knowledge of OAC. The increase of patient knowledge of OAC following an educational counselling was previously shown [181-184]. Education in these studies was based on educational content. We could conclude that even a simple screening with open-ended questions enables community pharmacists to easily counsel OAC patients.

The semi-structured interview we used consisted of eight questions which do not cover all educational domains important for OAC according to Wofford [61]. Because our study was not specific to VKA, topics such as blood-testing and food-drug interactions were omitted on purpose. Further, the presence of students as observer of a counselling with the amended PMC could have triggered community pharmacists to engage more in counselling practice than usual (also known as the Hawthorne effect [160]). In further studies, different sets of questions for either DOAC or VKA might be adequate and long-term sustainability of the increased knowledge of OAC and subsequent influence on behavior e.g., adherence and save use of medicines, need to be addressed in randomized controlled trials. Finally, the length of a counselling session with the amended PMC was rather long. Therefore, it may be reasonable to amend the PMC with specific questions only for high-risk medication such as OAC. We therefore suggest to further adapt the amended PMC to an "anticoagulation PMC", similar to the medicines use review in UK which was also adapted for specific target groups [159].

Research aiming to further develop medication review services in Swiss community pharmacy is ongoing. A current project concerns the development of the PMC to become a specific medication review for patients at hospital discharge [314]. Because the basic PMC is poorly implemented in daily practice, major adaptions are planned within this project. Likewise, the "anticoagulation PMC" could be improved with similar adaptions of the basic PMC protocol. Recently, a Swiss e-learning tool on oral anticoagulants was developed and is currently tested with pharmacy students [315].

The aim of this project is to prepare community pharmacists for patient education. To educate community pharmacists or other HPC might improve counselling quality, allow patient centered communication and decrease length of a counselling session.

In the **Study A-2**, we followed an evidence-based approach to select relevant items for patient knowledge of DOAC. After literature review, completeness of retrieved items were exhaustively verified and supplemented with the Swiss summaries of Product Characteristics (SPCs), the Update EHRA Practical Guide on the use of non-vitamin K antagonist anticoagulants [113], and the patient guide for taking DOAC from the cardiology patient page [170]. Twelve anticoagulation experts across different professions participated in the questionnaire development process to ensure content validity and the selection of relevant items. The developed Knowledge Of Direct Oral Anticoagulants (KODOA) test was validated in patients on DOAC and pharmacists. The KODOA-test confirmed to be feasible, comprehensive, reliable and valid to self-assess patient knowledge of DOAC. Construct validity was supported by significant differences in scores between patients and pharmacists. Finally, the KODOA-test was responsive to educational counselling about DOAC which supports construct validity.

We observed an internal consistency slightly lower than other knowledge assessment questionnaires. The obtained Cronbach's alpha value is likely to result from the multi-factorial nature of the KODOA-test because it consists of items derived from several education topics. The KODOA-test includes very easy items and very difficult items. Despite the fact that such grade of difficulty tends to decrease the internal consistency of the scale [175], we need basic questions on the medication that patient uses such as "Dosing frequency". Finally, a low Cronbach's alpha might be explained by the shortness of the KODOA-test with solely 15 questions, since internal consistency increases as test length increases [176]. With these considerations, an alpha of 0.67 seems acceptable. Stability over time was confirmed by test-retest correlation above the threshold of 0.7, which indicates adequate reliability [177]. Mean time between test and re-test was 12 days. Recommendations for interval between two identical tests vary between 2 days [175] and three months [178]. We selected a short time interval based on ethical consideration because patients with deficient knowledge should be corrected as soon as possible in order to avoid life threatening situations. Knowledge scores remained high after approximately two more weeks demonstrating the sustainability of the educational counselling. In addition, patients agreed uniformly that their knowledge had increased. Nevertheless, further follow-ups could be useful to maintain high level of knowledge.

A recent study investigating knowledge in OAC patients included patients with DOAC, but knowledge assessment method was not developed for patients on DOAC therapy [181]. Thus, an accurate measurement of patient knowledge of DOAC is still lacking. The KODOA-test could serve as reliable and valid knowledge assessment questionnaire for clinical trials. Whether the KODOA-test is applicable in other languages needs confirmation by further research.

The need to give special attention to patients on OAC has been recognized on an international level, i.e. the International Pharmacists for Anticoagulation Care Taskforce (iPACT) aims at providing high-quality care for patients receiving oral anticoagulation medication all around the world through high-quality training and counselling for pharmacists and healthcare practitioners [316]. **Studies A-1** and **A2** might contribute with important findings from Switzerland to the existing evidence and current investigations about patient knowledge on OAC on international level. **Project A** provides simple screening questions for the identification of knowledge gaps (**A-1**), a validated knowledge assessment questionnaire about DOAC and a standardized educational manual for counselling (**A-2**) for practice and research. How to best perform educational counselling e.g. spontaneous and unstructured counseling, counselling according to an education manual or another technique needs to be addressed in further studies. Additionally, studies are needed to proof efficacy, appropriateness and economics of an intervention with educational counselling.

Patient preferences and vitamin B12 deficiency

Project B consisted of three studies. The aim of the first study (**B-1**) was the assessment of the impact of type 2 diabetes (T2DM) and metformin use on VB12 associated biomarkers and their suitability to reflect VB12 supply. In a randomized controlled parallel group trial, we further aimed to compare early biomarker response and patient preferences to high dose oral and i.m. VB12 treatment with consideration of adherence issues (**B-2**). The last study (**B-3**) aimed to assess patient preferences for oral and parenteral treatment in various diseases through a literature review.

In Study B-1, differences of VB12, holotranscobalamine (HoloTc), the biologically active fraction %AB12=HoloTc/VB12*100 and homocystein (Hcy) were analysed i) among diabetic outpatients with (T2DMMet+) and without metformin use (T2DMMet-) and ii) in comparison to an external non-diabetic reference group with low levels of VB12 (<200pmol/L). We found that metformin treatment alone did not explain the altered VB12 metabolism as reflected by VB12 and HoloTc serum levels in all T2DM patients, as suggested by the literature [129, 201]. Nevertheless, proportion of patients in the DMMet+ group with low VB12, low HoloTc, or high Hcy was higher compared to DMMet- group (not significant). Additionally, metformin dosage did negatively correlate with VB12 and HoloTc levels. These findings suggest that metformin does influence VB12 metabolism. Further analysis focused on VB12-deficient subgroups and included non-diabetic patients. In this sample, a significant difference of the %AB12 was observed and confirmed by multiple regression analysis. However, the model explained only 9.2% of the variance observed. These results suggest that VB12 metabolism is affected by diabetes itself as well as by other factors, which were not included in the model. Thus, the reported data are not able to draw definitive conclusion about the impact of metformin use on VB12 associated biomarkers. We therefore suggest to assess the impact of T2DM, metformin use and other factors (e.g. age, duration of VB12 deficiency) on VB12 associated biomarkers in further studies.

HoloTc has been proposed as a better marker to detect VB12 deficiency compared to serum VB12 [207, 208] in an aged population [209]. We found significant inverse correlations of VB12 and HoloTc with Hcy, a functional marker of VB12 deficiency. Although the effect was stronger between VB12 and Hcy, compared to HoloTc and Hcy, stepwise multiple regression analysis included HoloTc as independent variable to explain variance in Hcy levels and not VB12. Thus, HoloTc seems more favorable than VB12 to predict hyperhomocysteinemia caused by VB12 deficiency in T2DM patients. Therefore, our results support the finding that HoloTc might be a better marker than VB12 to detect VB12 deficiency. Before recommending a change of current practice, further studies should include anemic patients and assess methylmalonic acid (MMA) levels to investigate the suitability of VB12 and HoloTc to represent VB12 supply in T2DM patients.

Study B-2 was a prospective randomized unblinded parallel group trial. Patients were recruited by their general practitioner and randomly assigned to oral or i.m. VB12 treatment. Group O-oral received oral daily 1000 µg cyanocobalamine for 28 days and group I-i.m. received 4 weekly injections of 1000 µg hydroxocobalamine. Blood samples were analyzed for VB12, HoloTc, Hcy and MMA. Before and after treatment, patients were asked to fill in a questionnaire about their preferences. After 28 days of treatment with high-dose VB12 administered either by oral or i.m. route, median levels of VB12-associated biomarkers were normalized. The majority of patients preferred oral treatment before and after the study.

Our findings are in line with other trials, of which two trials assessed the effect of oral high-dose VB12 substitution (1000 µg cyanocobalamin) vs. placebo [230, 233], while three other randomized, controlled trials compared cyanocobalamin therapy administered by oral (1000-2000 µg) or parenteral route (1000 µg cyanocobalamin) [228, 229, 234]. Contrary to prior studies, we observed an exaggerated response after i.m. administration and therefore the hypothesis for non-inferiority of oral in comparison to i.m. treatment had to be rejected. Because we used electronic punch cards and monitored an almost perfect intake of tablets (99.6% taking adherence), non-adherence could be ruled out as a contributor to the less pronounced response in VB12, HoloTc and Hcy in patients with oral administration. Thus, the enormous difference must have chemical or physiological reasons. One reason might be the use of hydroxocobalamine while other trials used cyanocobalamine for i.m. treatment. Hydroxocobalamine is a physiological intermediate form which shows a greater availability to cells than other cobalamin forms [235]. Thus, injection intervals for hydroxocobalamine and cyanocobalamine may differ.

Findings about biomarker levels after oral and i.m. treatment might add evidence to current practice of VB12 substitution. Current guidelines do not consider different cobalamine forms for the substitution of VB12 [122, 317]. The challenge is that cobalamine is recommended, but two different substances are available for parenteral application: “Cyano- and hydroxocobalamine”. Moreover, in some publications, both forms are falsely described equivalent (see Stabler SP, 2013 [130]: “*There are many recommended schedules for injections of vitamin B12 (called cyanocobalamin in the United States and hydroxocobalamin in Europe*”). Oral versus parenteral VB12 substitution is still under investigation by others: A large prospective randomized controlled trial comparing high dose oral vs intramuscular cyanocobalamin in elderly patients is currently being performed (PMID: 22650964, NCTNCT 01476007). This highlights the importance of the research field.

As expected, patients preferred oral treatment to i.m. treatment before the assignation to treatment as well as after its completion. Our findings are in line with reports from two studies on patient preferences on oral and parenteral VB12 treatment [240, 244] where the majority of patients preferred the oral route.

Although our study and others showed that patient majorly prefer oral substitution, no high-dose VB12 oral mono-preparation is currently available in Switzerland. Further, a discussion has emerged if the coenzyme forms methylcobalamine and adenosylcobalamine might be superior to cyano- and hydroxocobalamine [318]. It is unclear if an adequate oral VB12 formulation will soon be available for VB12 deficient patients in Switzerland. An alternative is offered by the import of VB12 containing mono-preparations from other countries such as Germany. In this case, insurance would not pay treatment what is likely to influence preferences. Therefore, adequate patient information is essential to come up with a final shared decision.

Limitations of **Studies B-1** and **B-2** arrived from the fact that we included patients mostly without hematological symptoms and not necessarily abnormal functional biomarkers, what affects our ability to generalize our results to a symptomatic, anemic population.

The literature review (**Study B3**) across different diseases yielded similar results: A majority of patients preferred oral treatment. Out of the 13 articles retrieved, five concerned cancer therapy, three antibiotic therapies, two vitamin deficiency and three other indications. Depending on the disease, oral or parenteral therapy was preferred. Given this and the availability of bioequivalent treatments for both therapy regimes, the evaluation of patient preferences may substantially add to treatment optimisation. Patients and physicians should take a shared decision for optional therapy regimens in order to promote individualized therapy and thus, have a major impact on cost-effectiveness.

Adherence assessment methods

In **Study C-1,** we aimed to validate the German version of the MMAS-8 in cardiovascular patients. We further aimed in **Study C-2** to evaluate whether one subjective question “Do you sometimes forget to take your medication?” that is contained in the PMC coincides with an objective adherence measure, the MPR.

The MMAS-8 [24] consists of seven yes/no questions and one 5-point Likert scale. The scale has demonstrated high internal consistency and good sensitivity and specificity, it is valid and reliable [24]. In **Study C-1,** the German version of the MMAS showed low psychometric properties compared with the original English MMAS-8, especially for internal consistency (Cronbach's alpha 0.31 vs. 0.83 [24]). The small to moderate reliability we observed is similar to that of three other studies that validated the French [251], Malaysian [29] and Thai [250] versions of the MMAS-8. Since Cronbach's alpha measures whether each item of a scale is appropriate for assessing the concept of the scale, the internal consistency of the entire scale will be high if all items measure the same phenomenon. In our case, we retained four components after varimax rotation that explained 71.7% of the variance (24.4% for the first component), indicating that the scale is four-dimensional. This is in contradiction with the original English scale that was declared one-dimensional [24], but in strong concordance with the results of the French and the Thai scales that attributed 55.2% and 57.4% of the variance, respectively, to three components [250, 251]. Consequently, the unacceptable low Cronbach's alpha in our study may indicate the multidimensionality of the scale rather than its inconsistency [277]. The MMAS-8D demonstrated convergent validity with electronic measures of adherence and with laboratory values. The correlation with electronic records, blood values and the significant association with BMQ subscores support the validity of the MMAS-8D. The latter is in accordance with findings from a study with women newly treated against osteoporosis with daily or weekly oral bisphosphonates, where the necessity subscore of the BMQ showed a significant association with the 8-item Morisky scale [280]. **Study C-1** provides as a by-product a validated adherence assessment questionnaire in German, the MMAS-8D.

After publication of **Study C-1**, the MMAS-8 had been translated in Polish [319] and was used in several international studies, such as one with patients with cystic fibrosis [320] or asthma [321]. These results suggest that the MMAS-8 is still widely used for adherence assessment. To date, studies using the German version of the MMAS-8 are ongoing [322] and are therefore expected to be published soon. However, due to copyright issues, we decided not to use the MMAS-8D in further projects. For subjective adherence assessment in **Project D,** we decided to use the "A14" adherence questionnaire [303] in its German version for which we obtained the rights.

A recent study [323] compared the MMAS-8, as a subjective adherence measure, and the MPR derived from pharmacy refill index, as an objective adherence measure, and observed poor accuracy of the MMAS-8 to identify objective medication non-adherence. In the pilot study of **Study C-2,** we compared the MPR from pharmacy refill data with one single objective question of the PMC. In line with the mentioned observations, congruence between subjective and objective assessment of adherence was poor, indicating that subjective measures and objective adherence assessment may capture different aspects of non-adherence.

Study proposal in anticoagulation

Finally, **Project D** aimed to develop a tailored and stepwise educational program on adherence to DOAC therapy in Switzerland. The development of the study proposal will speed up the study start in future. Other than in the previous projects on knowledge about OAC (Project A), educational counselling was planned to be offered repetitively according to patient needs. Additionally, visualizing of intake pattern obtained with the electronic monitoring should be employed for providing feedback and stressing the need of time adherence, or adapting the treatment plan in collaboration with the physician. The study realization and evaluation will be executed beyond of this thesis.

10.1 Limitations

Limitations specific to individual studies were discussed in previous sections. Overall limitations of this thesis were:

- Sample sizes of our studies were relatively small. Small sample sizes may limit the ability to generalize findings to all affected patients. Further, samples could be prone to selection bias. Motivated patients might have been more likely to accept participation and thereby patients were included who are more likely to be adherent and are probably better informed about treatment than the general population of outpatients. In particular, validation studies may have been affected by modest sample size, since small sample sizes can affect the result of the internal consistency.
- Patients enrolled in our studies were exclusively recruited in Switzerland, what may limit the applicability of our results to other countries and languages.
- The compiled questions used to assess patient preferences and the questions that were used to screen for knowledge gaps consisted of re-used questions from other assessment tools but were not validated completely as an entity.
- The observation periods included follow-up intervals from to 2 to 4 weeks to assess patient knowledge and preferences. We therefore cannot evaluate how knowledge or preference would change in long-term situation. The relatively brief adherence-monitoring period in Studies B-2 and C-1 may be criticized because it is insufficient to estimate overall adherence.
- Observer bias might have occurred leading to a bias in favor of the research hypotheses because one researcher was involved in development of study designs, collection of data, analysis and interpretation.
- Finally, our literature searches about patient preferences across different settings and knowledge about anticoagulation were made in 2013 and 2015, respectively. Because both research areas are highly debated topics, a greater number of articles might be available in the meantime. However, basic rules about knowledge and preferences will not change.

10.2 Conclusions

This thesis adds findings on the existing evidence of patient knowledge about OAC in outpatients, of patient preferences for VB12 therapy and of detection and treatment of VB12-deficient outpatients. Further, this thesis validated two questionnaires that can be used in future research or practice: the KODOA-test to self-assess patient knowledge of DOAC and the MMAS-8 in German to assess adherence.

The following conclusions could be drawn:

Patient knowledge about oral anticoagulation therapy

- A majority of outpatients show knowledge gaps concerning their therapy with OAC.
- Specific screening questions allow community pharmacists to detect deficient knowledge in short time and to provide spontaneous unstructured educational counselling when needed.
- The newly developed and validated KODOA-test showed good psychometric properties in Swiss elderly outpatients taking DOAC. Thus, the KODOA-test is a reliable and valid questionnaire to assess patient knowledge of DOAC.
- To our knowledge, the KODOA-test is the first validated questionnaire specific for patients taking DOAC and sensitive to change. Therefore, the KODOA-test could be used in clinical trials where associations between knowledge of DOAC and adherence or clinical outcomes are of interest.
- Patient knowledge increases after having received educational counselling either provided in an unstructured manner with the help of the amended PMC or in a structured and tailored manner after testing with the KODOA-test. Thus, the detection of knowledge gaps enable the provision of tailored patient counselling.
- Patients show high acceptance and state to be more confident about how to take their anticoagulant agent either after having received educational counselling provided spontaneously, in an unstructured manner with the help of the amended PMC or after educational counselling in a structured manner after testing with the KODOA-test. We therefore suggest that more outpatients could be approached for educational counselling about OAC.

Patient preferences and vitamin B12 deficiency

- The clinical biochemistry of VB12 in T2DM patients with scarce VB12 supply is modified in comparison to nondiabetic patients. This results in higher %AB12 due to reduced VB12 levels. It needs to be clarified in future research whether this effect is due to diabetes itself, metformin treatment and/ or a combination of other heath related situations.
- Assessment of HoloTc seems more favorable than VB12 to predict hyperhomocysteinemia caused by VB12 deficiency in T2DM patients. This may be a direct consequence of the modified %AB12 in T2DM patients which strengthens the recommendation to assess VB12 supply in clinical practice by measuring HoloTc.
- After oral and i.m. substitution with VB12, differences in VB12, HoloTc and Hcy levels between groups were higher than expected. Therefore, the hypothesis of non-inferiority of oral treatment had to be rejected. However, normalization of HoloTc and MMA was reached by all patients and normalization of VB12 and Hcy by the majority of patients within group O-oral after a one-month treatment. The clinical benefit of exaggerated biomarker response after i.m. treatment within a typical primary care population is questionable. Therapeutic schemes should be chosen with the consideration of mid-term biomarker effects and patient preferences.
- Initial rating in favor of either i.m. or oral therapy can change over time. However, the majority of patients preferred oral treatment before and after the study which highlights the need for a high dose oral VB12 preparation in Switzerland.

Adherence assessment methods

- The German MMAS-8D appears to be a reliable instrument to catch medication adherence in cardiovascular patients. Further, the MMAS-8D is endowed with simplicity and quickness of administration and scoring, which facilitates its use in several pathologies. It may be useful in patients with chronic therapy for detecting non-adherence.
- Combination of subjective and objective adherence measures may help to establish a more precise picture of (non-)adherence.

10.3 Outlook

According to the conclusions and findings of this thesis, recommendations for future research and practice are:

Patient knowledge about oral anticoagulation therapy

- The best way to counsel patients about OAC and association of increased patient knowledge about OAC with adherence and clinical outcomes should be assessed in further studies. **Project D** provides future researcher with a study proposal to investigate associations of increased patient knowledge about OAC and adherence.
- Patient opinions on counselling about OAC and acquisition of more knowledge of barriers and facilitators for patient-centred counselling should be of interest in further studies in order to ameliorate educational counselling in primary care setting.
- HCP in primary care should screen for deficient knowledge and provide educational counselling about OAC actively. The patient's whole therapy and his daily experiences should be included in the counselling in order to achieve patient centred counselling.
- In order to ensure continuous care in OAC patients, it may be helpful to provide different HCP with standardized screening questions and educational manuals about OAC counselling. Further, remuneration of counselling might increase implementation of such service in daily practice.

Patient preferences and vitamin B12 deficiency

- Assessment of HoloTc seems more favourable than VB12 to identify VB12-deficient patients. Whether these findings are restricted to T2DM patients should be assessed in further studies.
- The impact of T2DM, metformin use and other factors (e.g. age, duration of VB12 deficiency) on VB12 associated biomarkers should be investigated in further studies.
- Optimal injection interval for i.m. hydroxocobalamine is still to be defined. Weekly administration according to guidelines lead to exaggerated biomarker response in non-anemic patients. Consequently, lower injection frequency is very likely to be equivalent and thus makes treatment for patients more convenient and thereby influencing patient preferences.

- In practice, patient preferences should be assessed routinely before treatment initiation, across various diseases where equivalent treatment options exist. Repeated re-evaluation of patient preferences should be integrated while delivering continuous care because preferences might change over time.

Adherence assessment methods

- In practice, community pharmacists should screen for non-adherence by combining MPR from pharmacy refill data and subjective adherence assessment forms.
- The collaboration with IT specialists to integrate non-adherence alerts from refill data from pharmacy software could support community pharmacists in screening for non-adherence in daily practice.

11 Bibliography

1. WHO, *World Health Report 2003- Adherence to long-term therapies: evidence for action*, ed. W.H. Organization2003.
2. Hugtenburg, J.G., et al., *Definitions, variants, and causes of nonadherence with medication: a challenge for tailored interventions.* Patient Prefer Adherence, 2013. **7**: p. 675-82.
3. Vrijens, B., et al., *A new taxonomy for describing and defining adherence to medications.* Br J Clin Pharmacol, 2012. **73**(5): p. 691-705.
4. Sabaté, E., *Adherence to long-term therapies: evidence for action: World Health Organization; 2003.*
5. DiMatteo, M.R., *Variations in patients' adherence to medical recommendations: a quantitative review of 50 years of research.* Med Care, 2004. **42**(3): p. 200-9.
6. Gadkari, A.S. and C.A. McHorney, *Unintentional non-adherence to chronic prescription medications: how unintentional is it really?* BMC Health Serv Res, 2012. **12**: p. 98.
7. Britten, N., et al., *The expression of aversion to medicines in general practice consultations.* Soc Sci Med, 2004. **59**(7): p. 1495-503.
8. Soumerai, S.B., et al., *Cost-related medication nonadherence among elderly and disabled medicare beneficiaries: a national survey 1 year before the medicare drug benefit.* Arch Intern Med, 2006. **166**(17): p. 1829-35.
9. Tarn, D.M., et al., *Physician communication when prescribing new medications.* Arch Intern Med, 2006. **166**(17): p. 1855-62.
10. Coleman, E.A., et al., *The care transitions intervention: results of a randomized controlled trial.* Arch Intern Med, 2006. **166**(17): p. 1822-8.
11. Pound, P., et al., *Resisting medicines: a synthesis of qualitative studies of medicine taking.* Soc Sci Med, 2005. **61**(1): p. 133-55.
12. Munro, S.A., et al., *Patient adherence to tuberculosis treatment: a systematic review of qualitative research.* PLoS Med, 2007. **4**(7): p. e238.
13. Brown, T.M., et al., *Development of a conceptual model of adherence to oral anticoagulants to reduce risk of stroke in patients with atrial fibrillation.* J Manag Care Pharm, 2012. **18**(5): p. 351-62.
14. Ratanawongsa, N., et al., *Communication and medication refill adherence: the Diabetes Study of Northern California.* JAMA Intern Med, 2013. **173**(3): p. 210-8.
15. Eichler, H.-G., et al., *Bridging the efficacy–effectiveness gap: a regulator's perspective on addressing variability of drug response.* Nat Rev Drug Discov, 2011. **10**(7): p. 495-506.
16. Senst, B.L., et al., *Practical approach to determining costs and frequency of adverse drug events in a health care network.* Am J Health Syst Pharm, 2001. **58**(12): p. 1126-32.
17. McDonnell, P.J. and M.R. Jacobs, *Hospital admissions resulting from preventable adverse drug reactions.* Ann Pharmacother, 2002. **36**(9): p. 1331-6.
18. Osterberg, L. and T. Blaschke, *Adherence to medication.* N Engl J Med, 2005. **353**(5): p. 487-97.
19. Col, N., J.E. Fanale, and P. Kronholm, *The role of medication noncompliance and adverse drug reactions in hospitalizations of the elderly.* Arch Intern Med, 1990. **150**(4): p. 841-845.
20. Jeffery, R.A., et al., *Adherence measurement and patient recruitment methods are poor in intervention trials to improve patient adherence.* J Clin Epidemiol, 2014. **67**(10): p. 1076-82.
21. Morisky, D.E., L.W. Green, and D.M. Levine, *Concurrent and predictive validity of a self-reported measure of medication adherence.* Med Care, 1986. **24**(1): p. 67-74.

22. Shi, L., et al., *Concordance of adherence measurement using self-reported adherence questionnaires and medication monitoring devices.* Pharmacoeconomics, 2010. **28**(12): p. 1097-107.
23. Shalansky, S.J., A.R. Levy, and A.P. Ignaszewski, *Self-reported Morisky score for identifying nonadherence with cardiovascular medications.* Ann Pharmacother, 2004. **38**(9): p. 1363-8.
24. Morisky, D.E., et al., *Predictive validity of a medication adherence measure in an outpatient setting.* J Clin Hypertens (Greenwich), 2008. **10**(5): p. 348-54.
25. Oliveira-Filho, A.D., et al., *Association between the 8-item Morisky Medication Adherence Scale (MMAS-8) and blood pressure control.* Arq Bras Cardiol, 2012. **99**(1): p. 649-58.
26. Korb-Savoldelli, V., et al., *Validation of a French version of the 8-item Morisky medication adherence scale in hypertensive adults.* J Clin Hypertens (Greenwich), 2012. **14**(7): p. 429-34.
27. de Oliveira-Filho, A.D., et al., *The 8-item Morisky Medication Adherence Scale: validation of a Brazilian-Portuguese version in hypertensive adults.* Res Social Adm Pharm, 2014. **10**(3): p. 554-61.
28. Sakthong, P., R. Chabunthom, and R. Charoenvisuthiwongs, *Psychometric properties of the Thai version of the 8-item Morisky Medication Adherence Scale in patients with type 2 diabetes.* Ann Pharmacother, 2009. **43**(5): p. 950-7.
29. Al-Qazaz, H., et al., *The eight-item Morisky Medication Adherence Scale MMAS: translation and validation of the Malaysian version.* Diabetes Res Clin Pract, 2010. **90**(2): p. 216-21.
30. Sutton, S., et al., *Does electronic monitoring influence adherence to medication? Randomized controlled trial of measurement reactivity.* Ann Behav Med, 2014. **48**(3): p. 293-9.
31. Lehmann, A., et al., *Assessing medication adherence: options to consider.* Int J Clin Pharm, 2014. **36**(1): p. 55-69.
32. Burnier, M., et al., *Electronic compliance monitoring in resistant hypertension: the basis for rational therapeutic decisions.* J Hypertens, 2001. **19**(2): p. 335-41.
33. Arnet, I., P.N. Walter, and K.E. Hersberger, *Polymedication Electronic Monitoring System (POEMS) – a new technology for measuring adherence.* Frontiers in Pharmacology, 2013. **4**.
34. Arnet, I., et al., *A method for calculating adherence to polypharmacy from dispensing data records.* International Journal of Clinical Pharmacy, 2014. **36**(1): p. 192-201.
35. Martin, B.C., et al., *Contrasting measures of adherence with simple drug use, medication switching, and therapeutic duplication.* Ann Pharmacother, 2009. **43**(1): p. 36-44.
36. Messerli, M., et al., *Impact of a community pharmacist-led medication review on medicines use in patients on polypharmacy - a prospective randomised controlled trial.* BMC Health Services Research, 2016. **16**: p. 145.
37. Hatah, E., et al., *Retrospective examination of selected outcomes of Medicines Use Review (MUR) services in New Zealand.* Int J Clin Pharm, 2014. **36**(3): p. 503-12.
38. Hanna, J., *Real-world application of MedsCheck opportunities: The Costco pharmacists intervention trial for reduction of cardiovascular risk.* Can Pharm J (Ott), 2013. **146**(6): p. 325-8.
39. Castelino, R.L., B.V. Bajorek, and T.F. Chen, *Retrospective evaluation of home medicines review by pharmacists in older Australian patients using the medication appropriateness index.* Ann Pharmacother, 2010. **44**(12): p. 1922-9.
40. *Medication Therapy Management in community pharmacy practice: core elements of an MTM service (version 1.0).* J Am Pharm Assoc (2003), 2005. **45**(5): p. 573-9.
41. Latif, A., K. Pollock, and H.F. Boardman, *The contribution of the Medicines Use Review (MUR) consultation to counseling practice in community pharmacies.* Patient Educ Couns, 2011. **83**(3): p. 336-44.
42. van Dulmen, S., et al., *Patient adherence to medical treatment: a review of reviews.* BMC Health Serv Res, 2007. **7**: p. 55.

43. Haynes, R.B., et al., *Interventions to enhance medication adherence.* Cochrane Database Syst Rev, 2005(4): p. CD000011.
44. Nieuwlaat, R., et al., *Interventions for enhancing medication adherence.* Cochrane Database Syst Rev, 2014. **11**: p. CD000011.
45. Allemann, S.S., et al., *Congruence between patient characteristics and interventions may partly explain medication adherence intervention effectiveness: An analysis of 190 randomized controlled trials from a Cochrane systematic review.* J Clin Epidemiol, 2017.
46. Cushing, A. and R. Metcalfe, *Optimizing medicines management: From compliance to concordance.* Ther Clin Risk Manag, 2007. **3**(6): p. 1047-58.
47. *Health literacy: report of the Council on Scientific Affairs. Ad Hoc Committee on Health Literacy for the Council on Scientific Affairs, American Medical Association.* JAMA, 1999. **281**(6): p. 552-7.
48. Sørensen, K., et al., *Health literacy and public health: A systematic review and integration of definitions and models.* BMC Public Health, 2012. **12**(1): p. 80.
49. Pouliot, A. and R. Vaillancourt, *Medication Literacy: Why Pharmacists Should Pay Attention.* The Canadian Journal of Hospital Pharmacy, 2016. **69**(4): p. 335-336.
50. Ostini, R. and T. Kairuz, *Investigating the association between health literacy and non-adherence.* Int J Clin Pharm, 2014. **36**(1): p. 36-44.
51. *World Health Organization. Discussion paper on promoting, measuring and implementing health literacy: Implications for policy and practice in non-communicable disease prevention and control; 2017. Cited 2017 June 26, 2017.Available from: http://www.who.int/global-coordination-mechanism/working-groups/wg_33_2016_2017/en/.*
52. Laufs, U., V. Rettig-Ewen, and M. Bohm, *Strategies to improve drug adherence.* Eur Heart J, 2011. **32**(3): p. 264-8.
53. Custodis, F., et al., *Medication knowledge of patients hospitalized for heart failure at admission and after discharge.* Patient Prefer Adherence, 2016. **10**: p. 2333-2339.
54. Hunt, D.P., *The concept of knowledge and how to measure it.* Journal of intelectual Capital, 2003. **4**(1): p. 100-113.
55. Kalichman, S.C. and D. Rompa, *Functional health literacy is associated with health status and health-related knowledge in people living with HIV-AIDS.* J Acquir Immune Defic Syndr, 2000. **25**(4): p. 337-44.
56. Schillinger, D., et al., *Association of health literacy with diabetes outcomes.* JAMA, 2002. **288**(4): p. 475-82.
57. Williams, M.V., et al., *Relationship of functional health literacy to patients' knowledge of their chronic disease. A study of patients with hypertension and diabetes.* Arch Intern Med, 1998. **158**(2): p. 166-72.
58. *World Health Organization. Where are the patients in decision-making about their own care?; 2008. Cited 2017 June 26, 2017. Available from: http://apps.who.int/iris/handle/10665/107980.*
59. Bartlett, E.E., *At last, a definition.* Patient Educ Couns, 1985. **7**(4): p. 323-324.
60. Clarkesmith, D.E., H.M. Pattison, and D.A. Lane, *Educational and behavioural interventions for anticoagulant therapy in patients with atrial fibrillation.* Cochrane Database Syst Rev, 2013. **6**: p. CD008600.
61. Wofford, J.L., M.D. Wells, and S. Singh, *Best strategies for patient education about anticoagulation with warfarin: a systematic review.* BMC Health Serv Res, 2008. **8**: p. 40.
62. Michie, S., J. Miles, and J. Weinman, *Patient-centredness in chronic illness: what is it and does it matter?* Patient Educ Couns, 2003. **51**(3): p. 197-206.
63. Charlton, C.R., et al., *Nurse practitioners' communication styles and their impact on patient outcomes: an integrated literature review.* J Am Acad Nurse Pract, 2008. **20**(7): p. 382-8.
64. Wiederholt, J.B., B.R. Clarridge, and B.L. Svarstad, *Verbal consultation regarding prescription drugs: findings from a statewide study.* Med Care, 1992. **30**(2): p. 159-73.

65. Stevenson, F.A., et al., *Doctor-patient communication about drugs: the evidence for shared decision making.* Soc Sci Med, 2000. **50**(6): p. 829-40.
66. Richard, C. and M.T. Lussier, *Nature and frequency of exchanges on medications during primary care encounters.* Patient Educ Couns, 2006. **64**(1-3): p. 207-16.
67. Alkhawajah, A.M. and A.E. Eferakeya, *The role of pharmacists in patients' education on medication.* Public Health, 1992. **106**(3): p. 231-7.
68. Bell, H.M., J.C. McElnay, and C.M. Hughes, *A self-reported work sampling study in community pharmacy practice.* Pharm World Sci, 1999. **21**(5): p. 210-6.
69. McCann, L., C.M. Hughes, and C.G. Adair, *A self-reported work-sampling study in community pharmacy practice: a 2009 update.* Pharm World Sci, 2010. **32**(4): p. 536-43.
70. Davies, J.E., N. Barber, and D. Taylor, *What do community pharmacists do?: results from a work sampling study in London.* Int J Pharm Pract, 2014. **22**(5): p. 309-18.
71. van Dijk, M., et al., *Patient-provider communication about medication use at the community pharmacy counter.* Int J Pharm Pract, 2016. **24**(1): p. 13-21.
72. Boeni, F., I. Arnet, and K.E. Hersberger, *Adherence counseling during patient contacts in swiss community pharmacies.* Patient Prefer Adherence, 2015. **9**: p. 597-605.
73. Sleath, B., *Pharmacist-patient relationships: authoritarian, participatory, or default?* Patient Educ Couns, 1996. **28**(3): p. 253-63.
74. Chong, W.W., P. Aslani, and T.F. Chen, *Pharmacist-patient communication on use of antidepressants: a simulated patient study in community pharmacy.* Res Social Adm Pharm, 2014. **10**(2): p. 419-37.
75. Cumbler, E., H. Wald, and J. Kutner, *Lack of patient knowledge regarding hospital medications.* J Hosp Med, 2010. **5**(2): p. 83-6.
76. Holloway, A., *Patient knowledge and information concerning medication on discharge from hospital.* J Adv Nurs, 1996. **24**(6): p. 1169-74.
77. Rubio, J.S., et al., *Measurement of patients' knowledge of their medication in community pharmacies in Portugal.* Ciência & Saúde Coletiva, 2015. **20**: p. 219-228.
78. Alphonsa, A., et al., *Knowledge regarding oral anticoagulation therapy among patients with stroke and those at high risk of thromboembolic events.* J Stroke Cerebrovasc Dis, 2015. **24**(3): p. 668-72.
79. *Downing SM. Assessment of knowledge with written test forms. In: Norman GR, van der Vleuten CPM, Newble DI, eds, International Handbook of Research in Medical Education, Vol 2. Dordrecht, The Netherlands: Kluwer Academic Publishers; 2002:647–672.*
80. Ryan, R., et al., *Interventions to improve safe and effective medicines use by consumers: an overview of systematic reviews.* Cochrane Database Syst Rev, 2014(4): p. CD007768.
81. Wang, Y., et al., *Knowledge, satisfaction, and concerns regarding warfarin therapy and their association with warfarin adherence and anticoagulation control.* Thrombosis Research, 2014. **133**(4): p. 550-554.
82. Clarkesmith, D.E., et al., *Educational Intervention Improves Anticoagulation Control in Atrial Fibrillation Patients: The TREAT Randomised Trial.* PLoS ONE, 2013. **8**(9): p. e74037.
83. Brennan, P.F. and I. Strombom, *Improving health care by understanding patient preferences: the role of computer technology.* J Am Med Inform Assoc, 1998. **5**(3): p. 257-62.
84. Blinman, P., et al., *Preferences for cancer treatments: an overview of methods and applications in oncology.* Ann Oncol, 2012. **23**(5): p. 1104-10.
85. SE, S., et al., *Evidence Based Medicine How to Practice and Teach EBM*, ed. r. Edition2005, Edingurgh: Elsevier Churchill Livingstone. 1,12.
86. Melnyk, B. and E. Fineout-Overholt, *Evidence based practice in nursing and healthcare: A guide to best practice (3rd Edition)*2015: Philadelphia, PA:Wolters.

87. Wennberg, J.E., *Unwarranted variations in healthcare delivery: implications for academic medical centres.* BMJ, 2002. **325**(7370): p. 961-4.
88. Appelbaum, P.S. and T. Grisso, *Assessing patients' capacities to consent to treatment.* N Engl J Med, 1988. **319**(25): p. 1635-8.
89. Stevenson, F.A., et al., *A systematic review of the research on communication between patients and health care professionals about medicines: the consequences for concordance.* Health Expect, 2004. **7**(3): p. 235-45.
90. McKinstry, B., *Do patients wish to be involved in decision making in the consultation? A cross sectional survey with video vignettes.* BMJ, 2000. **321**(7265): p. 867-71.
91. McKeown, R.E., et al., *Shared decision making: views of first-year residents and clinic patients.* Acad Med, 2002. **77**(5): p. 438-45.
92. O'Connor, A.M., et al., *A survey of the decision-making needs of Canadians faced with complex health decisions.* Health Expect, 2003. **6**(2): p. 97-109.
93. Coulter, A., *Partnerships with patients: the pros and cons of shared clinical decision-making.* J Health Serv Res Policy, 1997. **2**(2): p. 112-21.
94. Makoul, G. and M.L. Clayman, *An integrative model of shared decision making in medical encounters.* Patient Educ Couns, 2006. **60**(3): p. 301-312.
95. Charles, C., A. Gafni, and T. Whelan, *Decision-making in the physician-patient encounter: revisiting the shared treatment decision-making model.* Soc Sci Med, 1999. **49**(5): p. 651-61.
96. Charles, C., T. Whelan, and A. Gafni, *What do we mean by partnership in making decisions about treatment?* BMJ, 1999. **319**(7212): p. 780-2.
97. Legare, F. and H.O. Witteman, *Shared decision making: examining key elements and barriers to adoption into routine clinical practice.* Health Aff (Millwood), 2013. **32**(2): p. 276-84.
98. Elwyn, G., D. Frosch, and S. Rollnick, *Dual equipoise shared decision making: definitions for decision and behaviour support interventions.* Implement Sci, 2009. **4**: p. 75.
99. Joosten, E.A.G., et al., *Systematic Review of the Effects of Shared Decision-Making on Patient Satisfaction, Treatment Adherence and Health Status.* Psychotherapy and Psychosomatics, 2008. **77**(4): p. 219-226.
100. Bowling, A. and S. Ebrahim, *Measuring patients' preferences for treatment and perceptions of risk.* Qual Health Care, 2001. **10 Suppl 1**: p. i2-8.
101. Kiesler, D.J. and S.M. Auerbach, *Optimal matches of patient preferences for information, decision-making and interpersonal behavior: evidence, models and interventions.* Patient Educ Couns, 2006. **61**(3): p. 319-41.
102. Lewin, S.A., et al., *Interventions for providers to promote a patient-centred approach in clinical consultations.* Cochrane Database Syst Rev, 2001(4): p. CD003267.
103. Duncan, E., C. Best, and S. Hagen, *Shared decision making interventions for people with mental health conditions.* Cochrane Database Syst Rev, 2010(1): p. CD007297.
104. Hack, T.F., et al., *Do patients benefit from participating in medical decision making? Longitudinal follow-up of women with breast cancer.* Psychooncology, 2006. **15**(1): p. 9-19.
105. O'Connor, A.M., et al., *Decision aids for people facing health treatment or screening decisions.* Cochrane Database Syst Rev, 2009(3): p. CD001431.
106. van der Weijden, T., et al., *How to integrate individual patient values and preferences in clinical practice guidelines? A research protocol.* Implementation Science : IS, 2010. **5**: p. 10-10.
107. Webb, D.G., R. Horne, and A.J. Pinching, *Treatment-related empowerment: preliminary evaluation of a new measure in patients with advanced HIV disease.* Int J STD AIDS, 2001. **12**(2): p. 103-7.
108. Zikria, J. and J. Ansell, *Oral anticoagulation with Factor Xa and thrombin inhibitors: Is there an alternative to warfarin?* Discov Med, 2009. **8**(43): p. 196-203.

109. Ageno, W., et al., *Oral anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines.* Chest, 2012. **141**(2 Suppl): p. e44S-e88S.
110. Kompendium, *Fachinformation Marcoumar des Arzneimittel-Kompendium Schweiz*, 19.02.2013.
111. Rosanio, S., et al., *Pharmacology, benefits, unaddressed questions, and pragmatic issues of the newer oral anticoagulants for stroke prophylaxis in non-valvular atrial fibrillation and proposal of a management algorithm.* International Journal of Cardiology, 2014. **174**(3): p. 471-483.
112. Cowell, R.P., *Direct oral anticoagulants: integration into clinical practice.* Postgrad Med J, 2014. **90**(1067): p. 529-39.
113. Heidbuchel, H., et al., *Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation.* Europace, 2015. **17**(10): p. 1467-507.
114. Solomon, L.R., *Disorders of cobalamin (vitamin B12) metabolism: emerging concepts in pathophysiology, diagnosis and treatment.* Blood Rev, 2007. **21**(3): p. 113-30.
115. Obeid, R., S.N. Fedosov, and E. Nexo, *Cobalamin coenzyme forms are not likely to be superior to cyano- and hydroxyl-cobalamin in prevention or treatment of cobalamin deficiency.* Mol Nutr Food Res, 2015. **59**(7): p. 1364-72.
116. Watanabe, F., *Vitamin B12 sources and bioavailability.* Exp Biol Med (Maywood), 2007. **232**(10): p. 1266-74.
117. Gille, D. and A. Schmid, *Vitamin B12 in meat and dairy products.* Nutr Rev, 2015. **73**(2): p. 106-15.
118. *DACH Referenzwerte auf http://www.dach-liga-homocystein.org/content/vitamin-b12 (last acsess 22.03.16)*.
119. Dali-Youcef, N. and E. Andres, *An update on cobalamin deficiency in adults.* QJM, 2009. **102**(1): p. 17-28.
120. Hvas, A. and E. Nexo, *Diagnosis and treatment of vitamin B12 deficiency--an update.* Haematologica, 2006. **91**(11): p. 1506-1512.
121. Andrès, E., et al., *Vitamin B(12) (cobalamin) deficiency in elderly patients.* CMAJ : Canadian Medical Association Journal, 2004. **171**(3): p. 251-259.
122. Schrier, S.L., *Diagnosis and treatment of vitamin B 12 and folic acid deficiency.* uptodate (online, last update 09/2016), 2016.
123. Stabler, S.P., *Vitamin B12 deficiency.* N Engl J Med, 2013. **368**(21): p. 2041-2.
124. Hvas, A.M. and E. Nexo, *Holotranscobalamin--a first choice assay for diagnosing early vitamin B deficiency?* J Intern Med, 2005. **257**(3): p. 289-98.
125. Nexo, E. and E. Hoffmann-Lücke, *Holotranscobalamin, a marker of vitamin B-12 status: analytical aspects and clinical utility.* Am J Clin Nutr, 2011. **94**(1): p. 359S-365S.
126. Yetley, E.A., et al., *Biomarkers of vitamin B-12 status in NHANES: a roundtable summary.* Am J Clin Nutr, 2011. **94**(1): p. 313S-321S.
127. Aparicio-Ugarriza, R., et al., *A review of the cut-off points for the diagnosis of vitamin B12 deficiency in the general population*, in *Clinical Chemistry and Laboratory Medicine (CCLM)*2015. p. 1149.
128. Solomon, L.R., *Diabetes as a cause of clinically significant functional cobalamin deficiency.* Diabetes Care, 2011. **34**(5): p. 1077-80.
129. Greibe, E., et al., *Metformin lowers serum cobalamin without changing other markers of cobalamin status: a study on women with polycystic ovary syndrome.* Nutrients, 2013. **5**(7): p. 2475-82.
130. Stabler, S.P., *Clinical practice. Vitamin B12 deficiency.* N Engl J Med, 2013. **368**(2): p. 149-60.
131. Albert Kind, F.M., *Vitamin B12 alle drei Monate substituieren ?* PrimaryCare 2008;8: Nr. 10, 2008.

132. van Walraven, C., P. Austin, and C.D. Naylor, *Vitamin B12 injections versus oral supplements. How much money could be saved by switching from injections to pills?* Can Fam Physician, 2001. **47**: p. 79-86.
133. *Swiss Agency for Therapeutic Products Swissmedic. Summary of Product Information, Available from URL: www.swissmedic.ch.*
134. Metaxas, C., et al., *Development and validation of a questionnaire to self-assess patient knowledge of direct oral anticoagulants (KODOA-test).* Drug Healthc Patient Saf, 2018. **10**: p. 69-77.
135. Metaxas, C., et al., *Impact of type 2 Diabetes and Metformin use on Vitamin B12 Associated Biomarkers - an Observational Study.* Exp Clin Endocrinol Diabetes, 2018. **126**(6): p. 394-400.
136. Metaxas, C., et al., *Early biomarker response and patient preferences to oral and intramuscular vitamin B12 substitution in primary care: a randomised parallel-group trial.* Swiss Med Wkly, 2017. **147**: p. w14421.
137. Metaxas, C., et al., *Oral versus parenteral route of application: The patients' perspective* 42nd ESCP symposium on clinical pharmacy: implementation of pharmacy practice; Prague, Czech Republic, 16-18 October 2013. Int J Clin Pharm. 2013;35(6):1251-351., 2013. **35**(6): p. 1251–1351.
138. Krousel-Wood, M., et al., *Development and evaluation of a self-report tool to predict low pharmacy refill adherence in elderly patients with uncontrolled hypertension.* Pharmacotherapy, 2013. **33**(8): p. 798-811.
139. Arnet, I., et al., *The 8-item Morisky Medication Adherence Scale translated in German and validated against objective and subjective polypharmacy adherence measures in cardiovascular patients.* J Eval Clin Pract, 2015. **21**(2): p. 271-7.
140. Metaxas, C., K.E. Hersberger, and I. Arnet, *Medication possession ratio may detect half of the self-declared non-adherent patients to direct oral anticoagulation treatment – A pilot study* 10th Pharmaceutical Care Network Europe (PCNE) Working conference: Build- Lead- Engage-Disseminate Bled, Slowenia, 1-4 February 2017.International Journal of Clinical Pharmacy;June 2017, Volume 39, Issue 3, pp 601–626.
141. Keeling, D., et al., *Guidelines on oral anticoagulation with warfarin – fourth edition.* Br J Haematol, 2011. **154**(3): p. 311-324.
142. Patel, M.R., et al., *Rivaroxaban versus warfarin in nonvalvular atrial fibrillation.* N Engl J Med, 2011. **365**(10): p. 883-91.
143. Buller, H.R., et al., *Oral rivaroxaban for the treatment of symptomatic pulmonary embolism.* N Engl J Med, 2012. **366**(14): p. 1287-97.
144. Heidbuchel, H., et al., *Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation.* Europace, 2015.
145. Salmela, B., et al., *Active online assessment of patients using new oral anticoagulants: bleeding risk, compliance, and coagulation analysis.* Semin Thromb Hemost, 2012. **38**(1): p. 23-30.
146. Chen, S.-Y., et al., *One-year adherence to Warfarin treatment for venous thromboembolism in high-risk patients and its association with long-term risk of recurrent events.* Journal of Managed Care Pharmacy, 2013. **19**(4): p. 291-301.
147. Rodriguez, R.A., M. Carrier, and P.S. Wells, *Non-adherence to new oral anticoagulants: a reason for concern during long-term anticoagulation?* J Thromb Haemost, 2013. **11**(2): p. 390-4.
148. Marcum, Z.A. and W.F. Gellad, *Medication Adherence to Multi-Drug Regimens.* Clinics in Geriatric Medicine, 2012. **28**(2): p. 287-300.
149. Boeni, F., et al., *Effect of drug reminder packaging on medication adherence: a systematic review revealing research gaps.* Syst Rev, 2014. **3**: p. 29.

150. Jin, J., et al., *Factors affecting therapeutic compliance: A review from the patient's perspective.* Ther Clin Risk Manag, 2008. **4**(1): p. 269-86.
151. Ledroit, M., *Direct oral anticoagulants : the impact of pharmaceutical interviews on patients' knowledge (Abstract)*, in *43rd Congress of the Europeon Society of Clinical Pharmacists*2014: Copenhagen.
152. Shrestha, S., et al., *Evaluation of patients' knowledge on warfarin in outpatient pharmacy of a tertiary care cardiac center.* BMC Research Notes, 2015. **8**: p. 429.
153. Chenot, J.-F., et al., *Safety relevant knowledge of orally anticoagulated patients without self-monitoring: a baseline survey in primary care.* BMC Fam Pract, 2014. **15**: p. 104-104.
154. Hernández Madrid, A., et al., *Differences in attitude, education, and knowledge about oral anticoagulation therapy among patients with atrial fibrillation in Europe: result of a self-assessment patient survey conducted by the European Heart Rhythm Association.* EP Europace, 2016. **18**(3): p. 463-467.
155. Griffith, L.E., et al., *Comparison of open and closed questionnaire formats in obtaining demographic information from Canadian general internists.* J Clin Epidemiol, 1999. **52**(10): p. 997-1005.
156. Janoly-Dumenil, A., et al., *Oral anticoagulant treatment - evaluating the knowledge of patients admitted in physical medicine and rehabilitation units.* Ann Phys Rehabil Med, 2011. **54**(3): p. 172-80.
157. Messerli, M., N. Vriends, and K.E. Hersberger, *Humanistic outcomes and patient acceptance of a pharmacist-led medication review in primary-care- a prospective randomised controlled trial.* Unpublished results.
158. Linn, A.J., et al., *Words that make pills easier to swallow: a communication typology to address practical and perceptual barriers to medication intake behavior.* Patient Prefer Adherence, 2012. **6**: p. 871-85.
159. MURs., P.S.N.C.P.N.t.g.f. http://psnc.org.uk/services-commissioning/advanced-services/murs/national-target-groups-for-murs/. Accessed 09.02.2017.
160. Delgado-Rodríguez, M. and J. Llorca, *Bias.* Journal of Epidemiology and Community Health, 2004. **58**(8): p. 635.
161. Weitz, J.I. and P.L. Gross, *New oral anticoagulants: which one should my patient use?* Hematology Am Soc Hematol Educ Program, 2012. **2012**: p. 536-40.
162. Kirchhof, P., et al., *2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS.* Eur Heart J, 2016. **37**(38): p. 2893-2962.
163. Olesen, J.B., et al., *Non-vitamin K antagonist oral anticoagulation agents in anticoagulant naive atrial fibrillation patients: Danish nationwide descriptive data 2011-2013.* Europace, 2015. **17**(2): p. 187-93.
164. Rodríguez-Bernal, C.L., et al., *Oral Anticoagulants Initiation in Patients with Atrial Fibrillation: Real-World Data from a Population-Based Cohort.* Frontiers in Pharmacology, 2017. **8**(63).
165. Mani, H. and E. Lindhoff-Last, *New oral anticoagulants in patients with nonvalvular atrial fibrillation: a review of pharmacokinetics, safety, efficacy, quality of life, and cost effectiveness.* Drug Des Devel Ther, 2014. **8**: p. 789-98.
166. Barcellona, D., P. Contu, and F. Marongiu, *Patient education and oral anticoagulant therapy.* Haematologica, 2002. **87**(10): p. 1081.
167. Zeolla, M.M., et al., *Development and validation of an instrument to determine patient knowledge: the oral anticoagulation knowledge test.* Ann Pharmacother, 2006. **40**(4): p. 633-8.
168. Briggs, A.L., et al., *The development and performance validation of a tool to assess patient anticoagulation knowledge.* Res Social Adm Pharm, 2005. **1**(1): p. 40-59.
169. Obamiro, K.O., L. Chalmers, and L.R. Bereznicki, *Development and Validation of an Oral Anticoagulation Knowledge Tool (AKT).* PLoS One, 2016. **11**(6): p. e0158071.

170. Lane, D.A. and K. Wood, *Cardiology patient page. Patient guide for taking the non-vitamin K antagonist oral anticoagulants for atrial fibrillation.* Circulation, 2015. **131**(16): p. e412-5.
171. *Devellis RF. Scale development: theory and applications. Newbury Park, CA: Sage Publications, 1991.*
172. Westen, D. and R. Rosenthal, *Quantifying construct validity: two simple measures.* J Pers Soc Psychol, 2003. **84**(3): p. 608-18.
173. *Bowling A. Research methods in health: investigation health and health services, 2nd edn. Buckingham: Open University Press, 2002*.
174. *Anastasi A: Psychological Testing, sixth edition New York, MacMillan; 1988.*
175. *Streiner EL and Norma GR: A Practical Guide to their development and Use. Oxford, Oxford University Press; 1989:39-52.*
176. Tavakol, M. and R. Dennick, *Making sense of Cronbach's alpha.* Int J Med Educ, 2011. **2**: p. 53-55.
177. Paiva, C.E., et al., *A critical analysis of test-retest reliability in instrument validation studies of cancer patients under palliative care: a systematic review.* BMC Med Res Methodol, 2014. **14**: p. 8.
178. Nunnally JC. Psychometrie theory. 2nd Ed. New York: McGraw-Hill.
179. Jones, A.M., et al., *Reliability and validity of nutrition knowledge questionnaire for adults.* J Nutr Educ Behav, 2015. **47**(1): p. 69-74.
180. Deniz, M.S. and A.A. Alsaffar, *Assessing the validity and reliability of a questionnaire on dietary fibre-related knowledge in a Turkish student population.* J Health Popul Nutr, 2013. **31**(4): p. 497-503.
181. Maikranz, V., et al., *Does a complex intervention increase patient knowledge about oral anticoagulation? - a cluster-randomised controlled trial.* BMC Fam Pract, 2017. **18**(1): p. 15.
182. Winans, A.R., K.M. Rudd, and D. Triller, *Assessing anticoagulation knowledge in patients new to warfarin therapy.* Ann Pharmacother, 2010. **44**(7-8): p. 1152-7.
183. Polek, C. and T. Hardie, *Warfarin use post hospitalization: pilot comparative effectiveness of telephone follow-up.* Rehabil Nurs, 2012. **37**(2): p. 80-7.
184. Vormfelde, S.V., et al., *Educating orally anticoagulated patients in drug safety: a cluster-randomized study in general practice.* Dtsch Arztebl Int, 2014. **111**(37): p. 607-14.
185. Kibirige, D. and R. Mwebaze, *Vitamin B12 deficiency among patients with diabetes mellitus: is routine screening and supplementation justified?* J Diabetes Metab Disord, 2013. **12**(1): p. 17.
186. Bergen, C. and C. Compher, *Total homocysteine concentration and associated cardiovascular and renal implications in adults.* J Cardiovasc Nurs, 2006. **21**(1): p. 40-6.
187. Pawlak, R., *Is Vitamin B12 Deficiency a Risk Factor for Cardiovascular Disease in Vegetarians?* American Journal of Preventive Medicine, 2015. **48**(6): p. e11-e26.
188. Nygard, O., et al., *Plasma homocysteine levels and mortality in patients with coronary artery disease.* N Engl J Med, 1997. **337**(4): p. 230-6.
189. Seshadri, S., et al., *Plasma homocysteine as a risk factor for dementia and Alzheimer's disease.* N Engl J Med, 2002. **346**(7): p. 476-83.
190. Wile, D.J. and C. Toth, *Association of metformin, elevated homocysteine, and methylmalonic acid levels and clinically worsened diabetic peripheral neuropathy.* Diabetes Care, 2010. **33**(1): p. 156-61.
191. Carlsen, S.M., *[Metformin and vitamin B 12 deficiency].* Tidsskr Nor Laegeforen, 2007. **127**(6): p. 764; author reply 764.
192. Sahin, M., et al., *Effects of metformin or rosiglitazone on serum concentrations of homocysteine, folate, and vitamin B12 in patients with type 2 diabetes mellitus.* J Diabetes Complications, 2007. **21**(2): p. 118-23.

193. Kilicdag, E.B., et al., *Administration of B-group vitamins reduces circulating homocysteine in polycystic ovarian syndrome patients treated with metformin: a randomized trial.* Hum Reprod, 2005. **20**(6): p. 1521-8.
194. Kancherla, V., et al., *Long-term Metformin Therapy and Monitoring for Vitamin B12 Deficiency Among Older Veterans.* J Am Geriatr Soc, 2017.
195. Liu, Q., et al., *Vitamin B12 status in metformin treated patients: systematic review.* PLoS One, 2014. **9**(6): p. e100379.
196. Bauman, W.A., et al., *Increased intake of calcium reverses vitamin B12 malabsorption induced by metformin.* Diabetes Care, 2000. **23**(9): p. 1227-31.
197. Inzucchi, S.E., et al., *Management of hyperglycaemia in type 2 diabetes, 2015: a patient-centred approach. Update to a Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes.* Diabetologia, 2015. **58**(3): p. 429-442.
198. Bosi, E., *Metformin--the gold standard in type 2 diabetes: what does the evidence tell us?* Diabetes Obes Metab, 2009. **11 Suppl 2**: p. 3-8.
199. de Jager, J., et al., *Long term treatment with metformin in patients with type 2 diabetes and risk of vitamin B-12 deficiency: randomised placebo controlled trial.* BMJ, 2010. **340**: p. c2181.
200. Leung, S., et al., *Metformin induces reductions in plasma cobalamin and haptocorrin bound cobalamin levels in elderly diabetic patients.* Clin Biochem, 2010. **43**(9): p. 759-60.
201. Greibe, E., et al., *Metformin increases liver accumulation of vitamin B12 - an experimental study in rats.* Biochimie, 2013. **95**(5): p. 1062-5.
202. Young, M.J., et al., *A multicentre study of the prevalence of diabetic peripheral neuropathy in the United Kingdom hospital clinic population.* Diabetologia, 1993. **36**(2): p. 150-4.
203. Reinstatler, L., et al., *Association of biochemical B(1)(2) deficiency with metformin therapy and vitamin B(1)(2) supplements: the National Health and Nutrition Examination Survey, 1999-2006.* Diabetes Care, 2012. **35**(2): p. 327-33.
204. Golding, P.H., *Holotranscobalamin (HoloTC, Active-B12) and Herbert's model for the development of vitamin B12 deficiency: a review and alternative hypothesis.* Springerplus, 2016. **5**(1): p. 668.
205. Baker, H., et al., *Cobalamin (vitamin B12) and holotranscobalamin changes in plasma and liver tissue in alcoholics with liver disease.* J Am Coll Nutr, 1998. **17**(3): p. 235-8.
206. Fragasso, A., et al., *Holotranscobalamin Is a Useful Marker of Vitamin B12 Deficiency in Alcoholics.* The Scientific World Journal, 2012. **2012**: p. 128182.
207. Nexo, E., et al., *Holo-transcobalamin is an early marker of changes in cobalamin homeostasis. A randomized placebo-controlled study.* Clin Chem, 2002. **48**(10): p. 1768-71.
208. Obeid, R. and W. Herrmann, *Holotranscobalamin in laboratory diagnosis of cobalamin deficiency compared to total cobalamin and methylmalonic acid.* Clin Chem Lab Med, 2007. **45**(12): p. 1746-50.
209. Valente, E., et al., *Diagnostic accuracy of holotranscobalamin, methylmalonic acid, serum cobalamin, and other indicators of tissue vitamin B(1)(2) status in the elderly.* Clin Chem, 2011. **57**(6): p. 856-63.
210. Sato, Y., et al., *Relationship between metformin use, vitamin B12 deficiency, hyperhomocysteinemia and vascular complications in patients with type 2 diabetes.* Endocr J, 2013. **60**(12): p. 1275-80.
211. Wollesen, F., et al., *Plasma total homocysteine and cysteine in relation to glomerular filtration rate in diabetes mellitus.* Kidney Int, 1999. **55**(3): p. 1028-35.
212. Hannibal, L., et al., *Biomarkers and Algorithms for the Diagnosis of Vitamin B12 Deficiency.* Front Mol Biosci, 2016. **3**: p. 27.
213. Ting, R., et al., *Risk factors of vitamin b12 deficiency in patients receiving metformin.* Arch Intern Med, 2006. **166**(18): p. 1975-1979.

214. Kancherla, V., et al., *Long-term Metformin Therapy and Monitoring for Vitamin B12 Deficiency Among Older Veterans.* J Am Geriatr Soc, 2017. **65**(5): p. 1061-1066.
215. Roy, R.P., et al., *Study of Vitamin B(12) deficiency and peripheral neuropathy in metformin-treated early Type 2 diabetes mellitus.* Indian Journal of Endocrinology and Metabolism, 2016. **20**(5): p. 631-637.
216. Ahmed, M.A., G. Muntingh, and P. Rheeder, *Vitamin B12 deficiency in metformin-treated type-2 diabetes patients, prevalence and association with peripheral neuropathy.* BMC Pharmacology & Toxicology, 2016. **17**: p. 44.
217. Chen, S., et al., *An observational study of the effect of metformin on B12 status and peripheral neuropathy.* The British Journal of Diabetes & Vascular Disease, 2012. **12**(4): p. 189-193.
218. Russo, G.T., et al., *Diabetic neuropathy is not associated with homocysteine, folate, vitamin B12 levels, and MTHFR C677T mutation in type 2 diabetic outpatients taking metformin.* J Endocrinol Invest, 2016. **39**(3): p. 305-14.
219. Wong, C.W., *Vitamin B12 deficiency in the elderly: is it worth screening?* Hong Kong Med J, 2015. **21**(2): p. 155-64.
220. Pflipsen, M.C., et al., *The Prevalence of Vitamin B12 Deficiency in Patients with Type 2 Diabetes: A Cross-Sectional Study.* The Journal of the American Board of Family Medicine, 2009. **22**(5): p. 528-534.
221. Tucker, K.L., et al., *Plasma vitamin B-12 concentrations relate to intake source in the Framingham Offspring study.* Am J Clin Nutr, 2000. **71**(2): p. 514-22.
222. Andres, E., et al., *Food-cobalamin malabsorption in elderly patients: clinical manifestations and treatment.* Am J Med, 2005. **118**(10): p. 1154-9.
223. Oh, R. and D.L. Brown, *Vitamin B12 deficiency.* Am Fam Physician, 2003. **67**(5): p. 979-86.
224. Herrmann, W., et al., *Vitamin B-12 status, particularly holotranscobalamin II and methylmalonic acid concentrations, and hyperhomocysteinemia in vegetarians.* Am J Clin Nutr, 2003. **78**(1): p. 131-6.
225. Snow, C.F., *Laboratory diagnosis of vitamin B12 and folate deficiency: a guide for the primary care physician.* Arch Intern Med, 1999. **159**(12): p. 1289-98.
226. Lam, J.R., et al., *Proton pump inhibitor and histamine 2 receptor antagonist use and vitamin B12 deficiency.* JAMA, 2013. **310**(22): p. 2435-42.
227. Dharmarajan, T.S., et al., *Do acid-lowering agents affect vitamin B12 status in older adults?* J Am Med Dir Assoc, 2008. **9**(3): p. 162-7.
228. Kuzminski, A.M., et al., *Effective Treatment of Cobalamin Deficiency With Oral Cobalamin.* Blood, 1998. **92**(4): p. 1191-1198.
229. Bolaman, Z., et al., *Oral versus intramuscular cobalamin treatment in megaloblastic anemia: a single-center, prospective, randomized, open-label study.* Clin Ther, 2003. **25**(12): p. 3124-34.
230. Favrat, B., et al., *Oral vitamin B12 for patients suspected of subtle cobalamin deficiency: a multicentre pragmatic randomised controlled trial.* BMC Fam Pract, 2011. **12**: p. 2.
231. Adachi, S., et al., *Enteral vitamin B12 supplements reverse postgastrectomy B12 deficiency.* Ann Surg, 2000. **232**(2): p. 199-201.
232. Vidal-Alaball, J., et al., *Oral vitamin B12 versus intramuscular vitamin B12 for vitamin B12 deficiency.* Cochrane Database Syst Rev, 2005(3): p. CD004655.
233. Eussen, S.J., et al., *Effect of oral vitamin B-12 with or without folic acid on cognitive function in older people with mild vitamin B-12 deficiency: a randomized, placebo-controlled trial.* Am J Clin Nutr, 2006. **84**(2): p. 361-70.
234. Castelli, M.C., et al., *Comparing the efficacy and tolerability of a new daily oral vitamin B12 formulation and intermittent intramuscular vitamin B12 in normalizing low cobalamin levels: a randomized, open-label, parallel-group study.* Clin Ther, 2011. **33**(3): p. 358-371 e2.

235. Hall, C.A., J.A. Begley, and P.D. Green-Colligan, *The availability of therapeutic hydroxocobalamin to cells.* Blood, 1984. **63**(2): p. 335-41.
236. Torsvik, I., et al., *Cobalamin supplementation improves motor development and regurgitations in infants: results from a randomized intervention study.* Am J Clin Nutr, 2013. **98**(5): p. 1233-40.
237. Chalmers, J.N. and N.K. Shinton, *Comparison of hydroxocobalamin and cyanocobalamin in the treatment of pernicious anaemia.* Lancet 1965 Dec 25;2(7426):1305-8.
238. Tillemans, M.P., et al., *Effect of administration route on the pharmacokinetics of cobalamin in elderly patients: a randomized controlled trial.* Curr Ther Res Clin Exp, 2014. **76**: p. 21-5.
239. Hertz, H., H.P. Kristensen, and E. Hoff-Jorgensen, *Studies on Vitamin B12 Retention. Comparison of Retention Following Intramuscular Injection of Cyanocobalamin and Hydroxocobalamin.* Scand J Haematol, 1964. **1**: p. 5-15.
240. Nyholm, E., et al., *Oral vitamin B12 can change our practice.* Postgrad Med J, 2003. **79**(930): p. 218-20.
241. Aparicio-Ugarriza, R., et al., *A review of the cut-off points for the diagnosis of vitamin B12 deficiency in the general population.* Clin Chem Lab Med, 2015. **53**(8): p. 1149-59.
242. Hvas, A.M. and E. Nexo, *Diagnosis and treatment of vitamin B12 deficiency--an update.* Haematologica, 2006. **91**(11): p. 1506-1512.
243. Pezacka, E., R. Green, and D.W. Jacobsen, *Glutathionylcobalamin as an intermediate in the formation of cobalamin coenzymes.* Biochem Biophys Res Commun, 1990. **169**(2): p. 443-50.
244. Kwong, J.C., et al., *Oral vitamin B12 therapy in the primary care setting: a qualitative and quantitative study of patient perspectives.* BMC Fam Pract, 2005. **6**(1): p. 8.
245. DiMatteo, M., *Variations in patients' adherence to medical recommendations: a quantitative review of 50 years of research.* Med Care, 2004. **42**(3): p. 200-9.
246. Arnet, I., P.N. Walter, and K.E. Hersberger, *Polymedication Electronic Monitoring System (POEMS) – a new technology for measuring adherence.* Front Pharmacol, 2013. **4**.
247. Horne, R., et al., *Understanding patients' adherence-related beliefs about medicines prescribed for long-term conditions: a meta-analytic review of the Necessity-Concerns Framework.* PLoS One, 2013. **8**(12): p. e80633.
248. de Oliveira-Filho, A., et al., *Association between the 8-item Morisky Medication Adherence Scale (MMAS-8) and blood pressure control.* Arquivos Brasileiros de Cardiologia, 2012. **99**(1): p. 649-58.
249. de Oliveira-Filho, A.D., et al., *The 8-item Morisky medication adherence scale: validation of a Brazilian–Portuguese version in hypertensive adults.* Research in Social and Administrative Pharmacy, 2013(0).
250. Sakthong, P., R. Chabunthom, and R. Charoenvisuthiwongs, *Psychometric properties of the Thai version of the 8-item Morisky Medication Adherence Scale in patients with type 2 diabetes.* Annals Pharmacother, 2009. **43**(5): p. 950-957.
251. Korb-Savoldelli, V., et al., *Validation of a French version of the 8-item Morisky Medication Adherence Scale in hypertensive adults.* J Clin Hypertens (Greenwich), 2012. **14**(7): p. 429-434.
252. Lee, G., et al., *Determinants of medication adherence to antihypertensive medications among a Chinese population using Morisky Medication Adherence Scale.* PLoS One, 2013. **8**(4): p. e62775.
253. Yan, J., et al., *Translation and validation of a Chinese version of the 8-item Morisky medication adherence scale in myocardial infarction patients.* J Eval Clin Pract, 2014.
254. Ude, M., et al., *Adherence to antihypertensives: feasibility of two self-report instruments to investigate medication-taking behaviour in German community pharmacies.* Int J Pharm Pract, 2013. **21**(3): p. 169-177.
255. Jank, S., et al., *The A14-scale: development and evaluation of a questionnaire for assessment of adherence and individual barriers.* Pharm World Sci, 2009.
256. Zok, K., *Einstellungen älterer Menschen zur Arzneimitteltherapie [Article in German].* WIdO-Monitor, 2012. **1**: p. 2012.

257. Petersen, J.J., et al., *Long-term effects of a collaborative care intervention on process of care in family practices in Germany: a 24-month follow-up study of a cluster randomized controlled trial.* Gen Hosp Psychiatry, 2014 [Epub Jul 22].
258. Hamann, G.F., et al., *Adherence to secondary stroke prevention Strategies – rsults from the German Stroke Data Bank.* Cardiovasc Dis, 2003. **15**(4): p. 282-288.
259. Roughead, E.E., et al., *Assessing overall duration of cardiovascular medicines in veterans with established cardiovascular disease.* Eur J Cardiovasc Prev Rehabil, 2010. **17**(1): p. 71-76.
260. Lehmann, A., et al., *Assessing medication adherence: options to consider.* Int J Clin Pharm, 2014. **36**(1): p. 55-69.
261. Stip, E., et al., *A randomized controlled trial with a Canadian electronic pill dispenser used to measure and improve medication adherence in patients with schizophrenia.* Front Pharmacol, 2013. **4**: p. 100.
262. Sutton, S., et al., *Does electronic monitoring influence adherence to medication? Randomized controlled trial of measurement reactivity.* Ann Behav Med, 2014: p. 1-7.
263. Shi, L., et al., *Concordance of adherence measurement using self-reported adherence questionnaires and medication monitoring devices.* Pharmacoeconomics, 2010. **28**(12): p. 1097-1107.
264. Horne, R., J. Weinman, and M. Hankins, *The beliefs about medicines questionnaire (BMQ): The development and evaluation of a new method for assessing the cognitive representation of medication.* Psychol Health, 1999. **14**(1): p. 1-24.
265. Walter, P., et al., *Antiplatelet resistance in outpatients with monitored adherence.* Platelets, 2013.
266. Wild, D., et al., *Principles of Good Practice for the translation and cultural adaptation process for Patient-Reported Outcomes (PRO) measures: report of the ISPOR Task Force for translation and cultural adaptation.* Value Health, 2005. **8**(2): p. 94-104.
267. Byer, B. and L. Myers, *Psychological correlates of adherence to medication in asthma.* Psychol Health Med, 2000. **5**(4).
268. Ross, S., A. Walker, and M.J. MacLeod, *Patient compliance in hypertension: role of illness perceptions and treatment beliefs.* J Hum Hypertens, 2004. **18**(9): p. 607-613.
269. Gauchet, A., C. Tarquinio, and G. Fischer, *Psychosocial predictors of medication adherence among persons living with HIV.* Int J Behav Med, 2007. **14**(3): p. 141-50.
270. Broadbent, E., L. Donkin, and J.C. Stroh, *Illness and treatment perceptions are associated with adherence to medications, diet, and exercise in diabetic patients.* Diabetes Care, 2011. **34**(2): p. 338-340.
271. Mahler, C., et al., *Patients' beliefs about medicines in a primary care setting in Germany.* J Eval Clin Pract, 2012. **18**(2): p. 409-413.
272. Zeller, A., K. Schroeder, and T.J. Peters, *An adherence self-report questionnaire facilitated the differentiation between nonadherence and nonresponse to antihypertensive treatment.* J Clin Epidemiol, 2008. **61**(3): p. 282-288.
273. Vrijens, B. and E. Goetghebeur, *Comparing compliance patterns between randomized treatments.* Control Clin Trials, 1997. **18**(3): p. 187-203.
274. Mega, J.L., et al., *Cytochrome P-450 polymorphisms and response to clopidogrel.* N Engl J Med, 2009. **360**(4): p. 354-362.
275. Larsen, S.B., et al., *Reduced antiplatelet effect of aspirin is associated with low-grade inflammation in patients with coronary artery disease.* Thromb Haemost, 2013. **109**(5): p. 920-929.
276. Leidy, N.K., D.A. Revicki, and B. GenestÖ, *Recommendations for evaluating the validity of quality of life claims for labeling and promotion.* Value Health, 1999. **2**(2): p. 113-127.
277. Schmitt, N., *Uses and abuses of coefficient alpha.* Psychol Assess 1996. **8**(6): p. 350-353.

278. Voils, C.I., et al., *Improving the measurement of self-reported medication nonadherence.* J Clin Epidemiol, 2011. **64**(3): p. 250-254.
279. Simoni, J.M., et al., *Self-report measures of antiretroviral therapy adherence: a review with recommendations for HIV research and clinical management.* AIDS Behav, 2006. **10**(3): p. 227-245.
280. Reynolds, K., et al., *Psychometric properties of the Osteoporosis-specific Morisky Medication Adherence Scale in postmenopausal women with osteoporosis newly treated with bisphosphonates.* Ann Pharmacother, 2012. **46**(5): p. 659-70.
281. Naderi, S.H., J.P. Bestwick, and D.S. Wald, *Adherence to drugs that prevent cardiovascular disease: meta-analysis on 376,162 patients.* Am J Med, 2012. **125**(9): p. 882-887.e1.
282. Wensing, M., et al., *Patient satisfaction with availability of general practice: an international comparison.* Int J Qual Health Care, 2002. **14**(2): p. 111-118.
283. Södergard, B., et al., *Differences in adherence and motivation to HIV therapy - two independent assessments in 1998 and 2002.* Int J Clin Pharm, 2006. **28**(4): p. 248-256.
284. Byerly, M.J., P.A. Nakonezny, and A.J. Rush, *The Brief Adherence Rating Scale (BARS) validated against electronic monitoring in assessing the antipsychotic medication adherence of outpatients with schizophrenia and schizoaffective disorder.* Schizophr Res, 2008. **100**(1-3): p. 60-69.
285. Panfil, E.-M., et al., *Conflict of interest with industry--a survey of nurses in the field of wound care in Germany, Australia and Switzerland [Article in German].* Pflege, 2014. **27**(3): p. 191-199.
286. Brenk-Franz, K., et al., *Validation of the German version of the patient activation measure 13 (PAM13-D) in an international multicentre study of primary care patients.* Plos One, 2013. **8**(9): p. e74786.
287. Yao, X., et al., *Effect of Adherence to Oral Anticoagulants on Risk of Stroke and Major Bleeding Among Patients With Atrial Fibrillation.* Journal of the American Heart Association: Cardiovascular and Cerebrovascular Disease, 2016. **5**(2): p. e003074.
288. Arnet, I., et al., *Proposal of Standardization to Assess Adherence With Medication Records: Methodology Matters.* Ann Pharmacother, 2016. **50**(5): p. 360-8.
289. Lloyd-Jones, D., et al., *Heart disease and stroke statistics--2010 update: a report from the American Heart Association.* Circulation, 2010. **121**(7): p. e46-e215.
290. Kannel, W.B., et al., *Epidemiologic features of chronic atrial fibrillation: the Framingham study.* N Engl J Med, 1982. **306**(17): p. 1018-22.
291. *National Institute for Health and Care Excellence. Atrial fibrillation: Management of atrial fibrillation.*, June 2014 [online]. Available from: www.nice.org.uk/guidance/cg180.
292. Laliberte, F., et al., *Impact of daily dosing frequency on adherence to chronic medications among nonvalvular atrial fibrillation patients.* Adv Ther, 2012. **29**(8): p. 675-90.
293. Carrothers, A.D., et al., *Patient-reported compliance with thromboprophylaxis using an oral factor Xa inhibitor (rivaroxaban) following total hip and total knee arthroplasty.* J Arthroplasty, 2014. **29**(7): p. 1463-7.
294. Crivera, C., et al., *Pharmacy quality alliance measure: adherence to non-warfarin oral anticoagulant medications.* Curr Med Res Opin, 2015: p. 1-21.
295. Petersen, M.L., et al., *Pillbox organizers are associated with improved adherence to HIV antiretroviral therapy and viral suppression: a marginal structural model analysis.* Clin Infect Dis, 2007. **45**(7): p. 908-15.
296. Messerli, M., Blozik E, Vriends N, Hersberger K.E., *Impact of a community pharmacist-led medication review on medicines use - a prospective randomised controlled trial* BMC Health Services Research, 2015 (submitted).
297. *http://www.venalink.co.uk/*.
298. Boeni, F., K.E. Hersberger, and I. Arnet, *Multidrug punch cards in primary care: a mixed methods study on patients' preferences and impact on adherence.* Frontiers in Pharmacology, 2014. **5**.

299. Walter, P.N., et al., *Antiplatelet resistance in outpatients with monitored adherence.* Platelets, 2014. **25**(7): p. 532-538.
300. Lee, J.K., K.A. Grace, and A.J. Taylor, *Effect of a pharmacy care program on medication adherence and persistence, blood pressure, and low-density lipoprotein cholesterol: A randomized controlled trial.* JAMA, 2006. **296**(21): p. 2563-2571.
301. Sturt, J.A., et al., *Effects of the Diabetes Manual 1:1 structured education in primary care.* Diabet Med, 2008. **25**(6): p. 722-31.
302. Maes K, T.R., Pichon R, Hersberger K, Lampert M., *Demonstrating the clinical pharmacist's activity: validation of a classification system for pharmaceutical interventions. International journal of clinical pharmacy.* Int J Clin Pharm (accepted), 2015.
303. Jank, S., et al., *The A14-scale: development and evaluation of a questionnaire for assessment of adherence and individual barriers.* Pharm World Sci, 2009. **31**(4): p. 426-31.
304. Baker, D.W., et al., *Development of a brief test to measure functional health literacy.* Patient Educ Couns, 1999. **38**(1): p. 33-42.
305. Connor, M., S. Mantwill, and P.J. Schulz, *Functional health literacy in Switzerland--validation of a German, Italian, and French health literacy test.* Patient Educ Couns, 2013. **90**(1): p. 12-7.
306. Cano, S.J., et al., *The Anti-Clot Treatment Scale (ACTS) in clinical trials: cross-cultural validation in venous thromboembolism patients.* Health Qual Life Outcomes, 2012. **10**: p. 120.
307. Ware, J., Jr., M. Kosinski, and S.D. Keller, *A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity.* Med Care, 1996. **34**(3): p. 220-33.
308. Muller-Nordhorn, J., S. Roll, and S.N. Willich, *Comparison of the short form (SF)-12 health status instrument with the SF-36 in patients with coronary heart disease.* Heart, 2004. **90**(5): p. 523-7.
309. Russell, C.L., et al., *Medication adherence patterns in adult renal transplant recipients.* Research in Nursing & Health, 2006. **29**(6): p. 521-532.
310. Heidbuchel, H., et al., *European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation.* Europace, 2013. **15**(5): p. 625-51.
311. Fitzpatrick, R., et al., *Evaluating patient-based outcome measures for use in clinical trials.* Health Technol Assess, 1998. **2**(14): p. i-iv, 1-74.
312. *http://www.blister-technik.de/*.
313. Amara, W., et al., *Patients' attitude and knowledge about oral anticoagulation therapy: results of a self-assessment survey in patients with atrial fibrillation conducted by the European Heart Rhythm Association.* Europace, 2016. **18**(1): p. 151-5.
314. Imfeld-Isenegger, T., et al., *EMILIA – e-Medication Plan After Hospital Discharge in Aargau: Design of an Observational Study, Conference Poster, Swiss Pharma Science Day, Switzerland 2017.*
315. Wentzky, V., et al., *Introduction of a Swiss E-learning Tool on Oral Anticoagulants to Pharmacy Students, Conference Poster, ESCP Symposium Heidelberg, Germany 2017.*
316. *http://www.ipact.org/ (accessed 18.08.2017)*.
317. Furger, P. and T. Suter, *Guidelines SURF-med©: Scientific-Units-Recommendations-Formulas: Guidelines Medizin der Schweiz: Editions D & F 2016.*
318. Thakkar, K. and G. Billa, *Treatment of vitamin B12 deficiency-methylcobalamine? Cyancobalamine? Hydroxocobalamin?-clearing the confusion.* Eur J Clin Nutr, 2015. **69**(1): p. 1-2.
319. Jankowska-Polanska, B., et al., *Psychometric properties of the Polish version of the eight-item Morisky Medication Adherence Scale in hypertensive adults.* Patient Prefer Adherence, 2016. **10**: p. 1759-66.
320. Knudsen, K.B., et al., *Associations between adherence, depressive symptoms and health-related quality of life in young adults with cystic fibrosis.* Springerplus, 2016. **5**(1): p. 1216.

321. Kovacevic M, e.a., *Impact of community pharmacists' interventions on asthma self-management care,Research in Social and Administrative Pharmacy (2017), http://dx.doi.org/10.1016/j.sapharm.2017.07.007*.
322. Weber, S., *Masterthesis: Re-evaluation of adherence to inhaled medication after an interventional study; University of Basel; 2017.*
323. de Castro, M.L., et al., *Assessing medication adherence in inflammatory bowel diseases. A comparison between a self-administered scale and a pharmacy refill index.* Rev Esp Enferm Dig, 2017. **109**(8): p. 542-551.

12 Appendix

The following appendix is limited to the main documents used within the various projects. For further information including all measurement instruments or raw data, please send a request to the author.

UNIVERSITÄT BASEL

20. Nov. 2015

DEPARTMENT OF PHARMACEUTICAL SCIENCES

Department of Pharmaceutical Sciences
Research Group PCRG
Klingelbergstrasse 50, CH-4056 Basel (Schweiz)

Tel

Mail corina.metaxas@unibas.ch Care
+41 061 267 15 19
Fax +41 061 267 14 28
Web www.pharmacare.unibas.ch

Die Ethikkommission
Nordwest- und Zentralschweiz
hat die vorliegenden Akten
☒ zur Kenntnis genommen
☑ genehmigt
Datum / Unterschrift
9.11.15

Ethikkommission EKNZ
Hebelstr. 53
4056 Basel

Basel, 19.11.15

Amendement: Durchführung einer Beobachtungsstudie im Rahmen einer Masterarbeit zur Identifikation von Pharmaceutical Care Issues in Patienten welche mit oralen Antikoagulantien behandelt werden

Ref Nr. EKBB: 50/12
„Evaluation 'Polymedikations-Check' - eine neue apothekenbasierte Dienstleistung mit - Fokus auf Compliance und die Medikamentenanwendung im Alltag"

Sehr geehrter Herr Prof. Perruchoud,

Die obengenannte Studie startete im Juni 2012 mit der Rekrutierung des ersten Patienten.
Am 14. April 2014 wurde die Datenerhebung mit der Entlassung des letzten Patienten aus der Studie abgeschlossen. Zu diesem Evaluationsprojekt konnte am 08.05.2015 ein umfassender Bericht dem Berufsverband als Auftraggeber übergeben werden. Ein Exemplar zu Ihren Akten liegt diesem Antrag ebenfalls bei – die Publikation der Resultate in wissenschaftlichen Journals ist eingeleitet. Wichtigste Ergebnisse dabei sind:

- Keine signifikante Verbesserung der objektiven Compliance (Primärer Outcome) zwischen Patienten mit einem PMC als Intervention vs. Kontrollgruppe ohne PMC.
- Signifikanter Einfluss auf subjektive Compliance unimittelbar nach der Intervention, positiver Trend über sämtliche Compliance-Messmethoden im Verlauf der Studie in der Interventionsgruppe.
- Die Studienpopulation zeigt sehr hohe Ausgangswerte für alle Zielparameter. Dies bedeutet, dass die ausschliesslich bezüglich Erfüllens der PMC-Kriterien selektionierten Patienten nur wenige Optimierungsmöglichkeiten bezüglich der gewählten Zielparameter zeigen.
- Hingegen zeigte sich der Trend dass Patienten mit Antithrombotika in der Interventionsgruppe bessere objektive Compliance aufwiesen als Patienten in der Kontrollgruppe (Medication possession ratio: 91.3%±16.3% Intervention vs. 85.4%±23.8%, p=0.119)

UNI BASEL

Wir möchten deshalb in einer Subanalyse einen „specialised PMC“ bei oral antikoagulierten Patienten, durchführen und erforschen. Ziel ist es, die Pharmaceutical Care Issues in dieser Patientengruppe zu identifizieren und entsprechende Massnahmen zu evaluieren (Patientenschulung). Diese Fortführung der Studie soll dazu dienen erste Erfahrungen mit einem specialised PMC zu sammeln und als Grundlage für eine fortführende Studie behilflich sein.

Entsprechend bitten wir um die Genehmigung der folgenden Anpassungen:

1. Da alle Patienten einen Anspruch auf bestmögliche Betreuung haben wird in der Beobachtungsstudie auf eine Kontrollgruppe verzichtet. Zudem sollen Patienten ad hoc rekrutiert werden, welche akut einen Bedarf für einen „specialized“ PMC aufweisen.
2. Der Follow-Up PMC wird nur dann zwingend durchgeführt, wenn aufgrund des ersten PMCs ein Bedarf durch den Apotheker festgestellt wird oder der Patient einen solchen wünscht. Follow-Up PMCs werden in der Studie nicht mehr zur Datenauswertung einbezogen.
3. Es wird nur ein Follow-Up Telefoninterview nach 1 bis maximal 4 Wochen geben.
4. Der jetzige PMC wird mit einem Interview zu medikamentenbezogenen Wissen und weiteren Fragen zur Adhärenz rund um die orale Antikoagulation aus publizierter Literatur erweitert[1, 2] (Siehe Beilage 1). Diese Änderung wirkt sich vornehmlich auf das zusätzliche Abfragen von Medikamentenbezogenem Wissen und dadurch auf die Datenauswertung aus.

Alle Studiendokumente wurden entsprechend der obengenannten Änderungen angepasst (siehe Beilagen).
Da dieses Projekt im Rahmen einer Masterarbeit ausgeführt wird, welche am 11. Januar 2016 starten wird, wären wir sehr dankar für eine baldige Antwort

Wir danken für die Prüfung unserer Eingabe und verbleiben
mit freundlichen Grüssen,

Basel, 19.11.2015

Prof. Kurt E. Hersberger

Literatur

1. *Doucette, W.R., et al., Development of the Drug Adherence Work-up (DRAW) tool. J Am Pharm Assoc (2003), 2012.* ***52****(6): p. e199-204.*
2. *Ledroit M. et al., Direct oral anticoagulants: the impact of pharmaceutical interviews on patients' knowledge. , Poster 43rd ESCP, Copenhagen, Denmark 2014.*

UNI BASEL

UNIVERSITÄT BASEL

Departement Pharmazeutische Wissenschaften
Pharmaceutical Care Research Group

ID Proband: _____ Datum: _____

ID Stud.Apot: _____ Visum: _____

Case Report Form(CRF)

Studie	Medication Review Focusing on Anticoagulation Therapy in Swiss Community Pharmacies (PMC-OAK)
Studienregister	ClinicalTrials.gov : NCT02703727
Studienzentrum	Pharmaceutical Care Research Group, Klingelbergstrasse 50, 4056 Basel
Principal Investigator	Prof. Kurt E Hersberger

T-0 Basisdaten Apotheke

Einschlusskriterien	Ja	Nein
• Geschäftsführer der Apotheke hat Einverständniserklärung verstanden und unterschrieben	☐	☐
Allgemeine Angaben		
• Kanton:		
• Zugehörigkeit: ☐ Kette ☐ Gruppierung ☐ Unabhängig		
• Falls nicht unabhängig, zugehörig wo: _____		

T-0 Basisdaten Proband

Einschlusskriterien	Ja	Nein
• ≥ 18 Jahre	☐	☐
• Verschreibung von ≥ 4 verschiedenen Medikamenten über ≥ 3 Monate	☐	☐
• Einnahme eines OAKs (Marcoumar, Xarelto, Eliquis, Pradaxa, Sintrom, Lixiana	☐	☐
	☐	☐
• Selbständiges Bereitstellen und Einnehmen der Medikamente	☐	☐
• Deutsche Sprache in Wort und Schrift	☐	☐
• Proband hat die Einverständniserklärung verstanden und unterschrieben	☐	☐
Allgemeine Angaben		
• Geschlecht: ☐m ☐w		
• Geburtsdatum: _____		

UNIVERSITÄT BASEL

Departement Pharmazeutische Wissenschaften
Pharmaceutical Care Research Group

ID Proband: _____ Datum: _____

ID Stud.Apot: _____ Visum: _____

CRF Teil 1

T-0 Fragebogen Patient

Allgemeine Angaben	Ja	Nein
• Fragebogen Patient ausgefüllt	☐	☐
• Anonymisiertes Fragebogen Patient dem Patientendossier beigelegt	☐	☐

T-0 History Patient

Allgemeine Angaben	Ja	Nein
• Anonymisierte History dem Dossier beigelegt	☐	☐
• Anonymisiertes Drug use Profile dem Dossier beigelegt	☐	☐

T-0 Intervention PMC-OAK

Allgemeine Angaben	Ja	Nein
• Anonymisiertes PMC Protokoll dem Patientendossier beigelegt	☐	☐
• Anonymisiertes Interview OAK dem Patientendossier beigelegt	☐	☐
• Anonymisierter Dokumentationsbogen dem Patientendossier beigelegt	☐	☐

- Datum PMC-OAK: ___/___/_____ (tt.dd.jjjj)
- Zeitbedarf in Minuten: _____
- Zeitbedarf Interview in Minuten: _____
- Welches orales Antikoagulanz (OAK): ☐ VKA ☐ NOAC
- OAK: Name,Stärke,Dosierung:_____
- Anzahl Medikamente verordnet: _____
- Anzahl Wissenslücken im Interview: _____
- Anzahl durchgeführter Interventionen aufgrund erkannter Wissenslücken: _____

UNIVERSITÄT BASEL

Departement Pharmazeutische Wissenschaften
Pharmaceutical Care Research Group

ID Proband: _____ Datum: _____

ID Stud.Apot: _____ Visum: _____

CRF Teil 2

T-1 Telefoninterview

Allgemeine Angaben	Ja	Nein
• Anonymisiertes Telefoninterview dem Dossier beigelegt	☐	☐

- Datum Telefoninterview: ___/___/_____ (tt.dd.jjjj)
- Tage seit PMC: _____
- Zeitbedarf in Minuten: _____
- Anzahl Wissenslücken im Telefoninterview: _____

UNIVERSITÄT BASEL

Departement Pharmazeutische Wissenschaften
Pharmaceutical Care Research Group

Klingelbergstrasse 50
CH-4056 Basel

Studienkoordination
Tel.+41 (0)61 267 15 29

SCHRIFTLICHE EINVERSTÄNDNISERKLÄRUNG DES PATIENTEN

zur Teilnahme an der Studie „Evaluation Polymedikations-Check – Medikamenten-anwendung im Alltag" Beobachtungsstudie bei oral antikoagulierten Patienten (Studiennummer EK 50/12)

- ☐ Ich wurde vom unterzeichnenden Apotheker ausführlich mündlich und schriftlich über die oben beschriebene Studie informiert und habe die Patienteninformation gelesen und verstanden. Alle meine Fragen wurden mir zufriedenstellend beantwortet.
- ☐ Ich hatte genügend Zeit, um meine Entscheidung zu treffen.
- ☐ Mit meiner Unterschrift bestätige ich meine Einwilligung zur freiwilligen Teilnahme. Ich kann meine Zustimmung jederzeit ohne Angabe von Gründen und ohne für mich daraus entstehende Nachteile für meine weitere Behandlung zurückziehen.
- ☐ Ich bin damit einverstanden, dass wissenschaftliches Personal des Departementes Pharmazie der Universität Basel oder der Studienapotheke im Zusammenhang mit dieser Studie Einsicht in meine medizinischen Daten nehmen darf.
- ☐ Eine Kopie der schriftlichen Patienteninformation und der Einverständniserklärung habe ich erhalten.

Name des Patienten / der Patientin in Druckschrift:	Geburtsdatum:	Geschlecht: ☐ weiblich ☐ männlich
Ort, Datum:	Unterschrift des Patienten / der Patientin:	
Telefonnummer:	ID Patient Wird von Studienapotheke ausgefüllt	

Bestätigung der/des Studienapotheker/in: Hiermit bestätige ich, dass ich diesem Patienten / dieser Patientin Wesen, Bedeutung und Tragweite der Studie erläutert habe. Ich versichere, alle im Zusammenhang mit dieser Studie stehenden Verpflichtungen zu erfüllen. Sollte ich zu irgendeinem Zeitpunkt während der Durchführung der Studie von Aspekten erfahren, welche die Bereitschaft des Patienten / der Patientin zur Teilnahme an der Studie beeinflussen könnten, werde ich ihn / sie umgehend darüber informieren.

Name der aufklärenden Studienapothekerin / des aufklärenden Studienapothekers	Stempel der Studienapotheke
Ort, Datum:	Unterschrift der aufklärenden Studienapothekerin / des aufklärenden Studienapothekers:

UNI BASEL

Polymedikations-Check

Name	Vorname	Pat.-Nr.
Str.	Ort	Tel.

Der Patient/die Patientin nimmt zurzeit täglich 4 oder mehr Medikamente auf ärztliche Verordnung und über längere Zeit (mind. 3 Monate) ein	☐
Der Patient/die Patientin ist einverstanden, dass der Apotheker/die Apothekerin einen Polymedikations-Check macht	☐
Geburtsdatum / /	Geschlecht ☐ männlich ☐ weiblich

1. Check Zeit Beginn: _____._____ Uhr

	Aktuelle Medikamente auf ärztliche Verordnung) (dieser Check basiert auf Informationen vom Patienten und/oder aus der Dokumentation der Apotheke)	Abklärung Bedarf für Beratung zur Anwendung dieses Medikamentes: Wissen, **wie**	Wissen, **weshalb**	**Vergessen** Sie manchmal dieses Medikament zu nehmen?	**Kommentare & weitere Angaben** (bei Bedarf Fortsetzung auf Rückseite)
	Name/ Stärke / Galenische Form neu ? ☐	Beratung ?	Beratung ?	Ja☐ Nein☐ Beratung ? ☐	
	Name/ Stärke / Galenische Form neu ? ☐	Beratung ?	Beratung ?	Ja☐ Nein☐ Beratung ? ☐	
	Name/ Stärke / Galenische Form neu ? ☐	Beratung ?	Beratung ?	Ja☐ Nein☐ Beratung ? ☐	
	Name/ Stärke / Galenische Form neu ? ☐	Beratung ?	Beratung ?	Ja☐ Nein☐ Beratung ? ☐	
	Name/ Stärke / Galenische Form neu ? ☐	Beratung ?	Beratung ?	Ja☐ Nein☐ Beratung ? ☐	
	Name/ Stärke / Galenische Form neu ? ☐	Beratung ?	Beratung ?	Ja☐ Nein☐ Beratung ? ☐	
	Name/ Stärke / Galenische Form neu ? ☐	Beratung ?	Beratung ?	Ja☐ Nein☐ Beratung ? ☐	
	Name/ Stärke / Galenische Form neu ? ☐	Beratung ?	Beratung ?	Ja☐ Nein☐ Beratung ? ☐	
	Name/ Stärke / Galenische Form neu ? ☐	Beratung ?	Beratung ?	Ja☐ Nein☐ Beratung ? ☐	

Selbstmedikation Ja☐ Nein☐ Auflistung mit Dosierung

☐ Kommentare / Fortsetzung auf Rückseite

2. Beratung

☐ Beratung zur Handhabung

3. Empfehlungen	Patient/in ist einverstanden	Kommentare:
☐Wochen-Dosiersystem durch den Apotheker	Ja ☐ Nein ☐	
☐Bedarf intensivierte Compliance-Unterstützung	Ja ☐ Nein ☐	
☐Bedarf Wiederholung Check in ……… Monaten	Ja ☐ Nein ☐	
☐Weiterleitung an Arzt/andere Fachperson	Ja ☐ Nein ☐	NAME Tel

☐Bedarf vertiefte Analyse (z.B. Wechselwirkungen, Nebenwirkungen, Duplikationen)

☐

☐

☐

Datum: ____ / ____ / 20___ Zeit Ende:____.____ Uhr	Stempel Apotheke /Unterschrift Apotheker/in:
Unterschrift Patient/in	

UNIVERSITÄT BASEL

Departement Pharmazeutische Wissenschaften
Pharmaceutical Care Research Group

Klingelbergstrasse 50
CH-4056 Basel

Studienkoordination
Tel.+41 (0)61 267 15 29

PMC Interviewguide: Fokus Antikoagulation

Matrikelnummer StudentIn _____ Start (Uhrzeit) _____

Fragen an den Patienten:

1 Fragen zum Blutverdünner	Antwort des Patienten:	Besteht Beratungsbedarf?
a) Bitte erzählen Sie mir wie Sie Ihren Blutverdünner einnehmen		☐ Ja ☐ Nein
b) Aufgrund welcher Erkrankung brauchen Sie einen Blutverdünner?		☐ Ja ☐ Nein
c) Wissen Sie, wie lange Sie den Blutverdünner noch einnehmen müssen?		☐ Ja ☐ Nein
d) Wie gehen Sie vor, wenn Sie bemerken, dass Sie vergessen haben eine Tablette einzunehmen?		☐ Ja ☐ Nein
e) Was sind die Folgen wenn Sie zu wenig Ihres Medikamentes einnehmen?		☐ Ja ☐ Nein
f) Was sind die Folgen wenn Sie zu viel Ihres Medikamentes einnehmen?		☐ Ja ☐ Nein
g) Wissen Sie warum Sie Ihren Zahnarzt, Arzt und Apotheker informieren sollten, dass Sie einen Blutverdünner einnehmen?		☐ Ja ☐ Nein
h) Haben Sie Bedenken, dass Ihr Blutverdünner Ihnen nicht hilft?		☐ Ja ☐ Nein
i) Denken Sie, dass Sie Ihren Blutverdünner nicht benötigen?		☐ Ja ☐ Nein
j) Hatten Sie Nebenwirkungen von Ihrem Blutverdünner?		☐ Ja ☐ Nein
k) Machen Sie sich Sorgen über Nebenwirkungen?		☐ Ja ☐ Nein

2 Fragen zur Polymedikation	Antwort des Patienten:	Besteht Beratungsbedarf?
a) Denken Sie, dass Sie zu viele Medikamente einnehmen müssen?		☐ Ja ☐ Nein
b) Wenn Sie reisen oder Ihr Zuhause verlassen, vergessen Sie manchmal Ihre Medikamente mitzunehmen?		☐ Ja ☐ Nein
c) Haben Sie Schluckbeschwerden?		☐ Ja ☐ Nein

UNIVERSITÄT BASEL

Departement Pharmazeutische Wissenschaften
Pharmaceutical Care Research Group

Klingelbergstrasse 50
CH-4056 Basel

Studienkoordination
Tel.+41 (0)61 267 15 29

d) Verändern Sie manchmal die Form ihrer Medikamente, um die Einnahme zu vereinfachen?		☐ Ja ☐ Nein

Bitte beantworten Sie diese Fragen selbst:

3 Fragen zum Patienten	Antwort:	Besteht Handlungsbedarf?
a) Haben Sie während dieses Interviews eine kognitive Einschränkung beim Patienten bemerkt?		☐ Ja ☐ Nein
b) Ist der Patient in seinen Alltagsaktivitäten so eingeschränkt, dass dies seine Adhärenz und/oder das Benutzen von Adhärenz-Hilfen (wie Dosett®) negativ beeinflusst?		☐ Ja ☐ Nein

Ende (Uhrzeit)

UNIVERSITÄT BASEL

Departement Pharmazeutische Wissenschaften
Pharmaceutical Care Research Group

Klingelbergstrasse 50
CH-4056 Basel

Studienkoordination
Tel.+41 (0)61 267 15 29

Telefon Interview: PMC Beobachtung Antikoagulation

Datum [tt.mm.jj]

Matrikelnummer StudentIn

Startzeit [hh:mm]

Einleitung und Einverständniserklärung

Guten Tag Herr/Frau ….. Mein Name ist …... Vor rund zwei Wochen haben wir uns im Zusammenhang mit dem Polymedikations-Check in der Apotheke kennengelernt. Nun möchte ich im Rahmen einer Forschungsarbeit gerne Ihre Eindrücke und Erfahrungen mit der neuen Dienstleistung auswerten. Sind Sie noch immer bereit einige Fragen diesbezüglich mit mir durchzugehen? ☐ **ja** ☐ **nein** Sie dürfen jederzeit und ohne Angabe von Gründen das Gespräch abbrechen und Ihre Antworten zurücknehmen. Selbstverständlich werden sämtliche Daten und Aussagen anonym ausgewertet und vertraulich behandelt.

1 Allgemeine Fragen zu Ihrem Blutverdünner

	JA	**NEIN**
a) Wissen Sie wie Ihr Blutverdünner heisst? **Falls ja,** er heisst: _____	☐	☐
b) Können Sie mir erklären wie Sie Ihren Blutverdünner einnehmen? **Falls ja,** bitte Antwort präzisieren : _____	☐	☐
c) Wissen Sie aufgrund welcher Erkrankung Sie Ihren Blutverdünner einnehmen sollen? **Falls ja,** bitte Antwort präzisieren :_____	☐	☐
d) Können Sie mir sagen wie lange Sie den Blutverdünner noch einnehmen müssen? **Falls ja,** bitte Antwort präzisieren: _____	☐	☐
e) Wissen Sie wie Sie vorgehen sollen wenn Sie vergessen Ihren Blutverdünner einzunehmen? **Falls ja,** bitte Antwort präzisieren: _____	☐	☐
f) Wissen Sie was passiert wenn Sie zu wenig von Ihrem Blutverdünner einnehmen (Unterdosierung)? **Falls ja,** bitte Antwort präzisieren: _____	☐	☐
g) Wissen Sie was passiert wenn Sie zu viel von Ihrem Medikament einnehmen (Überdosierung)? **Falls ja,** bitte Antwort präzisieren: _____	☐	☐
h) Wissen Sie, warum Sie Ihren Zahnarzt, Arzt und Apotheker informieren sollten, dass Sie einen Blutverdünner einnehmen? **Falls ja,** bitte Antwort präzisieren : _____	☐	☐

2 Rückmeldungen zur Beratung

Bitte beantworten Sie die folgenden Aussagen mit der Skala: **1** = stimme überhaupt nicht zu, **2** = stimme eher nicht zu, **3** = weder noch, **4** = stimme eher zu, **5** = stimme voll und ganz zu, **k.A.** = keine Angaben.

Seit dem Gespräch mit dem Apotheker…	**1**	**2**	**3**	**4**	**5**	**k.A.**
a …habe ich **weniger Bedenken,** dass mein Blutverdünner mir **nicht** hilft.	☐	☐	☐	☐	☐	☐
b …bin ich **überzeugter** davon, dass ich **meinen Blutverdünner benötige.**	☐	☐	☐	☐	☐	☐
c …mache ich mir **weniger Sorgen** wegen der Nebenwirkungen meines Blutverdünners.	☐	☐	☐	☐	☐	☐
d …**vergesse ich seltener** meinen Blutverdünner einzunehmen.	☐	☐	☐	☐	☐	☐
e … Fühle ich mich **sicherer** in der Anwendung mit meinem Blutverdünner	☐	☐	☐	☐	☐	☐
f … habe ich **mehr Vertrauen** in meinen Blutverdünner	☐	☐	☐	☐	☐	☐
g Der/die Apotheker/in konnte **meine Fragen** zu meiner Zufriedenheit beantworten.	☐	☐	☐	☐	☐	☐
h Ich würde diese Dienstleistung weiter empfehlen.	☐	☐	☐	☐	☐	☐

Haben Sie **noch Fragen** zu der Therapie mit Ihrem Blutverdünner? **Falls ja,** bitte Antwort präzisieren:_____

Vielen Dank für die Teilnahme an dieser Umfrage! → **Endzeit** [hh:mm]:

Das Telefoninterview hat dazu geführt, dass der Patient erneut zu einer Beratung in die Apotheke eingeladen wurde: ☐ **ja** ☐ **nein**

UNIVERSITÄT BASEL

Departement Pharmazeutische Wissenschaften
Pharmaceutical Care Research Group

Klingelbergstrasse 50
CH-4056 Basel

Studienkoordination
Tel.+41 (0)61 267 15 29

Matrikelnummer StudentIn: _____ Datum: _____

Kommentar Polymedikations-Check:
Im PMC-Gespräch wurden Empfehlungen zum Therapieplan abgegeben. Begründen und kommentieren Sie diese bitte aus klinisch-pharmazeutischer Perspektive (Änderungen im Therapieplan, Medikamentenmanagement mit Wochendispenser, arzneimittelbezogene Probleme):

ID	Kurze Beschreibung der Intervention	
	Hintergrund	
	Grund der Intervention	
	Intervention	
	Resultat der Intervention	
	Hintergrund	
	Grund der Intervention	
	Intervention	
	Resultat der Intervention	
	Hintergrund	
	Grund der Intervention	
	Intervention	
	Resultat der Intervention	

	Hintergrund	
	Grund der Intervention	
	Intervention	
	Resultat der Intervention	
	Hintergrund	
	Grund der Intervention	
	Intervention	
	Resultat der Intervention	
	Hintergrund	
	Grund der Intervention	
	Intervention	
	Resultat der Intervention	

Hat der PMC zu weiteren Aktivitäten / Abklärungen geführt?

☐ Nein ☐ Ja → *bitte beschreiben und kommentieren Sie diese kurz:*

Herzlichen Dank für Ihre Mitarbeit!

Ethikkommission Nordwest- und Zentralschweiz EKNZ

Frau
Dr. Isabelle Arnet
Pharmaceutical Care Research Group
Pharmazentrum
Klingelbergstrasse 50
4058 Basel

Basel, 25. Januar 2016 / cb

EKNZ UBE-15/126:
Entwicklung und Validierung eines neuen Schulungsprogramms für Patienten mit neuen oralen Gerinnungshemmern

Sehr geehrte Frau Dr. Arnet

Besten Dank für Ihr Schreiben datiert vom 14. Dezember 2015 samt Beilagen, welches am 23. Dezember 2015 bei uns eingetroffen ist. Die Ethikkommission Nordwest- und Zentralschweiz hat die Dokumente zum oben genannten Projekt zur Kenntnis genommen und nimmt nun wie folgt Stellung:

Unsere Abklärungen haben ergeben, dass es sich um keine bewilligungspflichtige Studie im Sinne der kantonalen und eidgenössischen Gesetzgebung handelt. Aus diesem Grund kann die EKNZ keine förmliche Bewilligung ausstellen. Nach Überprüfung der Anfrage kann die EKNZ jedoch feststellen, dass die Durchführung dieser Studie aus ethischer Sicht unbedenklich ist (vgl. Art. 51 Abs. 2 Humanforschungsgesetz).

Ich hoffe, Ihnen mit diesen Angaben zu dienen und verbleibe

mit freundlichen Grüssen

i. V.

Prof. A. P. Perruchoud
Präsident der Ethikkommission
Nordwest- und Zentralschweiz / EKNZ

Geschäftsführerin: Frau Irene Oberli, Hebelstrasse 53, 4056 Basel, Telefon 061 268 13 50, Fax 061 268 13 51, eknz@bs.ch. www.eknz.ch

UNIVERSITÄT BASEL

Departement Pharmazeutische Wissenschaften
Pharmaceutical Care Research Group

ID Proband: _____ Datum: _____

ID Stud.Apot: _____ Visum: _____

Case Report Form(CRF)

Studie	**Entwicklung und Validierung eines neuen Schulungsprogramms für Patienten mit neuen oralen Gerinnungshemmern (NOACs)**
Ethik Nr	UBE-15/126
Studienzentrum	Pharmaceutical Care Research Group, Klingelbergstrasse 50, 4056 Basel
Principal Investigator	Dr.Isabelle Arnet

Basisdaten Proband

Allgemeine Angaben		
• Geschlecht: ☐m ☐w		
Einschlusskriterien	**Ja**	**Nein**
• ≥ 18 Jahre	☐	☐
• Einnahme eines NOACs: Xarelto, Eliquis, Pradaxa, Sintrom, Lixiana	☐	☐
• Deutsche Sprache in Wort und Schrift	☐	☐
• Indikation des NOACs ist entweder **Vorhofflimmern** ☐ oder **Lungenembolie/Tiefe Venenthrombose** ☐	☐	☐

V-1: Erster Besuch

Entnehmen Sie den Studienunterlagen 1 Dossier für Vorhofflimmern oder Lungenembolie/Tiefe Venenthrombose. Übertragen Sie die Patientenidentifikationsnummer auf dem Dossier auf das CRF. Entnehmen Sie die Mappe beschriftet mit **Visit 1** und lassen Sie die Dokumente vom Patienten in nachstehender Reihenfolge ausfüllen.

Visit 1	Ja	Nein
1) Einverständniserklärung		
• Der Proband hat die Einverständniserklärung verstanden und unterschrieben	☐	☐
• Eine Kopie der Einverständniserklärung wurde angefertigt und dem Patienten mitgegeben	☐	☐
• Die Rückseite der Einverständniserklärung wurde vom informierenden Apotheker unterschrieben	☐	☐
2) Fragebogen Patient		
• Der Patient füllt den Fragebogen „Patient“ aus	☐	☐
3) Fragebogen „NOAC Wissen“		
• Händigen Sie den Fragebogen aus und notieren Sie: **Zeit (Start): Datum:**		
• Der Patient hat den Fragebogen selbständig ausgefüllt	☐	☐
• Notieren Sie die Zeit sobald der Patient fertig ist **Zeit (Ende):**		
4) Fragebogen „Verständlichkeit“		
• Der Proband hat den Fragebogen „Verständlichkeit“ ausgefüllt	☐	☐

UNIVERSITÄT BASEL

Departement Pharmazeutische Wissenschaften
Pharmaceutical Care Research Group

ID Proband: _____ Datum: _____

ID Stud.Apot: _____ Visum: _____

Abschluss Visit 1

Bevor Sie den Probanden entlassen, vereinbaren Sie einen Termin für den zweiten Besuch und vergewissern Sie, dass Sie die richtige Adresse und Telefonnummer des Probanden haben.

„Die erste Befragung ist nun zu Ende, nun sollten wir einen Termin in der nächsten Woche vereinbaren. An diesem Termin erhalten Sie eine Schulung zu Ihrem Blutverdünner, dies wird ungefähr 15-20 Minuten dauern, wann haben Sie Zeit? “

Abschluss Visit 1	Ja	Nein
• Ein Termin für den nächsten Besuch wurde vereinbart **Datum:** **Zeit:**	☐	☐
• Die Adresse und Telefonnummer des Probanden wurden überprüft	☐	☐
• Eine Adressetikette wurde ausgedruckt und im Dossier dem Mäppchen Follow-UP beigelegt	☐	☐
• Alle Dokumente wurden vom Patienten zurückerhalten und ins Mäppchen Visit 1 zurückgelegt ➢ Einverständniserklärung ➢ Fragebogen Patient ➢ Fragebogen NOAC ➢ Fragebogen Verständlichkeit ➢ CRF Teil 1	☐	☐

Notizen

UNIVERSITÄT BASEL

Departement Pharmazeutische Wissenschaften
Pharmaceutical Care Research Group

ID Proband: _____ Datum: _____

ID Stud.Apot: _____ Visum: _____

V-2: Zweiter Besuch

Allgemeine Angaben	Ja	Nein
• Der Proband ist am vereinbarten Termin erschienen	☐	☐
• **Datum: Zeit:**		
• Der Proband ist an einem anderen Termin erschienen:	☐	☐
• **Datum: Zeit:**		
• Der Proband ist nicht mehr erschienen:	☐	☐
• Grund:		

Entnehmen Sie das Dossier des Probanden und entnehmen Sie die Mappe beschriftet mit **Visit 2.** Lassen Sie die Dokumente vom Patienten in nachstehender Reihenfolge ausfüllen.

Visit 2	Ja	Nein
1) Fragebogen „NOAC Wissen“ **Nummer 1**		
• Der Patient hat den Fragebogen selbständig ausgefüllt	☐	☐
2) Schulung **Nummer 2**		
• Sie haben mit dem Dokument „Schulung“ gezielt die Wissenslücken des Patienten gefüllt	☐	☐
• **Dauer Schulung (min):**		
3) Fragebogen „NOAC Wissen“ **Nummer 3**		
• Der Patient hat den Fragebogen selbständig ausgefüllt	☐	☐

*„**Haben Sie noch Fragen** zu Ihrem Blutverdünner oder Ihren anderen Medikamenten?“*

Ja ☐ *Nein* ☐ *(Falls Ja unter Notizen notieren)*

„Möchten Sie einen Blutverdünner-Ausweis mitnehmen?“ Ja ☐ *Nein* ☐

Abschluss Visit 2

„Vielen Dank dass Sie an unserer Befragung teilgenommen haben. Sie werden nächste Woche einen Brief mit dem 10.- Reka Check als Dankeschön erhalten. Zusätzlich sind 2 Fragebogen enthalten, unter anderem weil wir gerne wissen möchten, was Sie von der heutigen Schulung halten. Wir würden uns freuen wenn Sie diese auch noch ausfüllen würden.

Abschluss Visit 2	Ja	Nein
• Der Follow UP Brief sollte spätestens an diesem Datum versendet werden: **Datum:**	☐	☐
• Alle Dokumente wurden vom Patienten zurückerhalten und ins Mäppchen Visit 2 zurückgelegt	☐	☐
➢ Fragebogen NOAC Nummer 1	☐	☐
➢ Fragebogen NOAC Nummer 2	☐	☐
➢ CRF Teil 2		

UNIVERSITÄT BASEL

Departement Pharmazeutische Wissenschaften
Pharmaceutical Care Research Group

ID Proband: _____ Datum: _____

ID Stud.Apot: _____ Visum: _____

Studienabschluss

Entnehmen Sie dem Dossier des Probanden die Mappe beschriftet mit **Follow UP.**

Follow UP Brief	Ja	Nein
• Kleben Sie die Adresse des Probanden auf das vorfrankierte Couvert	☐	☐
• Unterschreiben Sie den Dankesbrief an den Patienten, füllen Sie seinen Namen ein und legen Sie diesen Brief ins Couvert	☐	☐
• Werfen Sie den Brief in 4-5 Tagen ein, damit er am vorgesehenen Datum ankommt	☐	☐
• Eingeworfen am: **Datum:**		
Studienunterlagen		
• Schreiben Sie die Adressen und Telefonnummer des Probanden auf ein separates Blatt	☐	☐
• Senden Sie an das Studienzentrum ➢ Mäppli 1 ➢ Mäppli 2 ➢ Leeres Mäppli 3 ➢ Seperate Adresse und Telefonnummer des Patienten ➢ Anonymisierte History des Patienten der letzten 12 Monate	☐	☐

Notizen

Falls zutreffend, ungefähre Dauer Beratung zu anderen Medikamenten (min):

UNIVERSITÄT BASEL

DEPARTMENT OF PHARMACEUTICAL SCIENCES

Department of Pharmaceutical Sciences
Pharmaceutical Care Research Group PCRG
Klingelbergstrasse 50, CH-4056 Basel (Schweiz)

Dr. Isabelle Arnet
Tel

Mail isabelle.arnet@unibas.ch
+41 061 207 15 67
Fax +41 061 207 14 28
Web pharmacare.unibas.ch

Schriftliche Einverständniserklärung zur Teilnahme an einer Studie

- Bitte lesen Sie dieses Formular sorgfältig durch.
- Bitte fragen Sie, wenn Sie etwas nicht verstehen oder wissen möchten.

Nummer der Studie: (bei der zuständigen Ethikkommission)	UBE-15/126
Titel der Studie:	**"Entwicklung und Validierung eines neuen Schulungsprogramms für Patienten mit neuen oralen Gerinnungshemmern (NOACs)"**
verantwortliche Institution (Sponsor) (vollständige Adresse):	Prof. Kurt E. Hersberger Klingelbergstrasse 50, 4056 Basel
Ort der Durchführung:	Kantonsspital Bruderholz Baselland/Apotheken Baselland/Baselstadt/Solothurn
Leiter / Leiterin der Studie am Studienort Name und Vorname in Druckbuchstaben:	Dr. Isabelle Arnet Klingelbergstrasse 50, 4056 Basel
Teilnehmerin/Teilnehmer Name und Vorname in Druckbuchstaben: Geburtsdatum:	_____ _____ ☐ weiblich ☐ männlich

- Ich wurde vom unterzeichnenden Arzt/Ärztin/Prüfperson mündlich und schriftlich über den Zweck, den Ablauf der Studie, über die zu erwartenden Wirkungen, über mögliche Vor- und Nachteile sowie über eventuelle Risiken informiert.
- Meine Fragen im Zusammenhang mit der Teilnahme an dieser Studie sind mir zufriedenstellend beantwortet worden. Ich kann die schriftliche Studieninformation vom 09.06.2016/ Version 4 behalten und erhalte eine Kopie meiner schriftlichen Einwilligungserklärung. Ich akzeptiere den Inhalt der zur oben genannten Studie abgegebenen schriftlichen Studieninformation.
- Ich nehme an dieser Studie freiwillig teil. Ich kann jederzeit und ohne Angabe von Gründen meine Zustimmung zur Teilnahme widerrufen, ohne dass ich deswegen Nachteile bei der weiteren medizinischen Betreuung erleide.
- Ich hatte genügend Zeit, meine Entscheidung zu treffen.
- Ich möchte dass der Hausarzt über meine Teilnahme an der Studie informiert wird:
  ja ☐ nein ☐ Wenn ja: Name/Ort: _____
- Ich weiss, dass meine persönlichen Daten nur in verschlüsselter Form zu Forschungszwecken weitergegeben werden können. Ich bin einverstanden, dass die zuständigen Fachleute des Auftraggebers der Studie in meine Originaldaten Einsicht nehmen dürfen, jedoch unter strikter Einhaltung der Vertraulichkeit.

Ort, Datum	Unterschrift Studienteilnehmerin/Studienteilnehmer

UNIVERSITÄT BASEL

DEPARTMENT OF PHARMACEUTICAL SCIENCES

Department of Pharmaceutical Sciences
Pharmaceutical Care Research Group PCRG
Klingelbergstrasse 50, CH-4056 Basel (Schweiz)

Dr. Isabelle Arnet
Tel

Mail isabelle.arnet@unibas.ch
+41 061 207 15 67
Fax +41 061 207 14 28
Web pharmacare.unibas.ch

Bestätigung des Studienapothekers: Hiermit bestätige ich, dass ich dieser Teilnehmerin/diesem Teilnehmer Wesen, Bedeutung und Tragweite der Studie erläutert habe. Ich versichere, alle im Zusammenhang mit dieser Studie stehenden Verpflichtungen gemäss dem geltenden Recht zu erfüllen. Sollte ich zu irgendeinem Zeitpunkt während der Durchführung der Studie von Aspekten erfahren, welche die Bereitschaft der Teilnehmerin/des Teilnehmers zur Teilnahme an der Studie beeinflussen könnten, werde ich sie/ihn umgehend darüber informieren.

Ort, Datum	Name und Vorname der informierenden StudienapothekerIn/ des informierenden Studienapothekers/ der informierenden Prüfperson in Druckbuchstaben Unterschrift der Studienapothekerin/des Studienapothekers

Universität Basel
Departement Pharmazeutische Wissenschaften
Pharmaceutical Care Research Group PCRG
Klingelbergstrasse 50, CH-4056 Basel (Schweiz)
DEPARTMENT OF PHARMACEUTICAL SCIENCES

Patientenfragebogen zu neuen Blutverdünnern

Sehr geehrte Patientin, Sehr geehrter Patient

Vielen Dank, dass Sie an unserer Befragung teilnehmen. Wir haben 15 Fragen zum Thema „neue Blutverdünner" für Sie vorbereitet. Das Ausfüllen dauert ungefähr 10 Minuten.
Bitte beantworten Sie die Fragen:

- Indem Sie das Kästchen ☐ bei der Antwort ankreuzen, welche Sie für richtig halten.
- Bitte kreuzen Sie pro Frage nur 1 Kästchen an.
- Wenn Sie sicher sind, dass Sie die richtige Antwort angekreuzt haben, kreuzen Sie zusätzlich bei der Frage „ich bin mir sicher" ☐ Ja an.
- Falls Sie unsicher sind, oder raten mussten, kreuzen Sie bitte ☐ Nein an.

Der/die Apotheker/In wird Ihnen im Anschluss Ihre Fragen beantworten.

1. Wie heisst Ihr Blutverdünner?	
☐ Eliquis®	☐Xarelto®
☐ Pradaxa®	☐Lixiana®

Ich bin mir sicher ☐ Ja ☐ Nein

2. Wie lange müssen Sie Ihren Blutverdünner einnehmen?	
☐ Maximal 2 Wochen	☐ mindestens bis zum nächsten Arzttermin
☐ Maximal 4 Wochen	

Ich bin mir sicher ☐Ja ☐Nein

3. Wie oft sollen Sie Ihren Blutverdünner einnehmen?	
☐Einmal täglich	☐Morgens und abends
☐Morgens, mittags und abends	

Ich bin mir sicher ☐Ja ☐Nein

4. Vor was schützt Sie Ihr Blutverdünner?	
☐ Vor Schwindel	☐ Vor hohem Blutdruck
☐ Vor einem Schlaganfall	

Ich bin mir sicher ☐Ja ☐Nein

5. Stellen Sie sich vor, Sie **wissen nicht mehr**, ob Sie Ihren Blutverdünner schon eingenommen haben. Wie gehen Sie vor?	
☐ Eine Tablette / Kapsel einnehmen, ausser die nächste geplante Einnahme steht unmittelbar bevor	☐Keine Tablette / Kapsel einnehmen, und mit der nächsten Dosis wie geplant fortfahren
☐Eine halbe Tablette / den halben Inhalt einer Kapsel einnehmen	

Ich bin mir sicher ☐Ja ☐Nein

6. Stellen Sie sich vor, Sie haben heute die letzte Einnahme von ihrem Blutverdünner **vergessen**. Wie gehen Sie vor?	
☐ Die Einnahme innerhalb von 6 Stunden nachholen	☐ Die Einnahme innerhalb von 12 Stunden nachholen
☐ Die Einnahme nicht nachholen	

Ich bin mir sicher ☐Ja ☐Nein

7. Stellen Sie sich vor, Sie haben **heute aus Versehen doppelt so viele** Tabletten / Kapseln eingenommen. Wie gehen Sie vor?	
☐ Die nächste Einnahme wie gewohnt einnehmen	☐ Die nächsten 2 Einnahmen auslassen
☐ Die nächste Einnahme auslassen	

Ich bin mir sicher ☐Ja ☐Nein

8. Stellen Sie sich vor, Sie haben vor 5 Minuten Ihren Blutverdünner eingenommen und mussten jetzt erbrechen. Ist die Wirkung Ihres Blutverdünners schwächer?	
☐ Nein, der Blutverdünner wirkt trotzdem	☐ Ja, der Blutverdünner wirkt nicht
☐ Nein, erst wenn man ein zweites Mal erbrechen muss, wirkt der Blutverdünner schlechter	

Ich bin mir sicher ☐Ja ☐Nein

9. Welches ist eine mögliche Nebenwirkung Ihres Blutverdünners?	
☐ Blaue Flecken	☐ Haarausfall
☐ Fusspilz	

Ich bin mir sicher ☐Ja ☐Nein

10. Welches freiverkäufliche Schmerz- und Fiebermittel ist bei der Einnahme Ihres Blutverdünners am Sichersten?	
☐Acetylsalicylsäure (z.B. Aspirin®)	☐Paracetamol (z.B. Dafalgan®)
☐Ibuprofen (z.B. Algifor®)	

Ich bin mir sicher ☐Ja ☐Nein

11. Sie möchten freiverkäufliche Medikamente einnehmen und wissen nicht, ob die Wirkung ihres Blutverdünners beeinflusst wird. Mit wem nehmen Sie am besten Rücksprache?	
☐ Beim Hersteller des Blutverdünners	☐Beim Arzt / Apotheker
☐ Bei Freunden / Familie	

Ich bin mir sicher ☐Ja ☐Nein

12. In welcher Situation sollten Sie Ihren Arzt informieren, dass Sie einen Blutverdünner einnehmen?	
☐Vor einer geplanten Operation (inkl. Eingriff beim Zahnarzt)	☐Vor einer Röntgenuntersuchung
☐Vor einer Blutdruckmessung	

Ich bin mir sicher ☐Ja ☐Nein

13. In welcher Situation sollten Sie noch am selben Tag Ihre/n Ärztin/Arzt kontaktieren oder den Notfall aufsuchen?	
☐Bei Husten mit blutigem Auswurf	☐Bei einer schmerzhaften Schürfwunde
☐ Bei Übelkeit und Brechreiz	

Ich bin mir sicher ☐Ja ☐Nein

14. Wie oft sollten Sie sich wegen Ihrem Blutverdünner für Kontrolluntersuchungen bei Ihrem Arzt melden?	
☐Alle 1-2 Wochen	☐ Mindestens 1 mal im Jahr
☐ Alle 1-2 Monate	

Ich bin mir sicher ☐Ja ☐Nein

15. Was sollten Sie immer bei sich tragen, wenn Sie einen Blutverdünner einnehmen?	
☐Verbandsmaterial	☐Blutverdünner-Ausweis
☐Blutspende-Ausweis	

Ich bin mir sicher ☐Ja ☐Nein

Vielen Dank für's Ausfüllen !

Universität Basel
Departement Pharmazeutische Wissenschaften
Pharmaceutical Care Research Group PCRG
Klingelbergstrasse 50, CH-4056 Basel (Schweiz)
DEPARTMENT OF PHARMACEUTICAL SCIENCES

Patientenfragebogen zu neuen Blutverdünnern

Sehr geehrte Patientin, Sehr geehrter Patient

Vielen Dank, dass Sie an unserer Befragung teilnehmen. Wir haben 15 Fragen zum Thema „neue Blutverdünner" für Sie vorbereitet. Das Ausfüllen dauert ungefähr 10 Minuten.
Bitte beantworten Sie die Fragen:

- Indem Sie das Kästchen ☐ bei der Antwort ankreuzen, welche Sie für richtig halten.
- Bitte kreuzen Sie pro Frage nur 1 Kästchen an.
- Wenn Sie sicher sind, dass Sie die richtige Antwort angekreuzt haben, kreuzen Sie zusätzlich bei der Frage „ich bin mir sicher" ☐ Ja an.
- Falls Sie unsicher sind, oder raten mussten, kreuzen Sie bitte ☐ Nein an.

Der/die Apotheker/In wird Ihnen im Anschluss Ihre Fragen beantworten.

1. Wie heisst Ihr Blutverdünner?	
☐ Eliquis®	☐Xarelto®
☐ Pradaxa®	☐Lixiana®

Ich bin bei der Antwort sicher ☐Ja ☐Nein

2. Wie lange müssen Sie Ihren Blutverdünner einnehmen?	
☐Maximal 2 Wochen	☐ Mindestens bis zum nächsten Arzttermin
☐Maximal 1 Jahr	

Ich bin bei der Antwort sicher ☐Ja ☐Nein

3. Wie oft täglich sollten Sie Ihren Blutverdünner einnehmen?	
☐Einmal täglich	☐Morgens und abends
☐Die ersten 3 Wochen lang morgens und abends, danach eine höhere Dosis nur noch 1 mal täglich	

Ich bin bei der Antwort sicher ☐Ja ☐Nein

4. Vor was schützt Sie ihr Blutverdünner?	
☐ Vor Schwindel	☐ Vor hohem Blutdruck
☐ Vor einer Thrombose/ Lungenembolie	

Ich bin bei der Antwort sicher ☐Ja ☐Nein

5. Stellen Sie sich vor, Sie **wissen nicht mehr**, ob Sie Ihren Blutverdünner schon eingenommen haben. Wie gehen Sie vor?	
☐Eine Tablette / Kapsel einnehmen, ausser die nächste geplante Einnahme steht unmittelbar bevor	☐Keine Tablette / Kapsel einnehmen, und mit der nächsten Dosis wie geplant fortfahren
☐Eine halbe Tablette / den halben Inhalt einer Kapsel einnehmen	

Ich bin bei der Antwort sicher ☐Ja ☐Nein

6. Stellen Sie sich vor, Sie haben heute die letzte Einnahme von ihrem Blutverdünner **vergessen**. Wie gehen Sie vor?	
☐ Die Einnahme innerhalb von 6 Stunden nachholen	☐ Die Einnahme innerhalb von 12 Stunden nachholen
☐ Die Einnahme nicht nachholen	

Ich bin bei der Antwort sicher ☐Ja ☐Nein

7. Stellen Sie sich vor, Sie haben **heute aus Versehen doppelt so viele** Tabletten / Kapseln eingenommen. Wie gehen Sie vor?	
☐ Die nächste Einnahme wie gewohnt einnehmen	☐ Die nächsten 2 Einnahmen auslassen
☐ Die nächste Einnahme auslassen	

Ich bin bei der Antwort sicher ☐Ja ☐Nein

8. Stellen Sie sich vor, Sie haben vor 5 Minuten Ihren Blutverdünner eingenommen und mussten jetzt erbrechen. Ist die Wirkung Ihres Blutverdünners schwächer?	
☐ Nein, der Blutverdünner wirkt trotzdem	☐ Ja, der Blutverdünner wirkt nicht
☐ Nein, erst wenn man ein zweites Mal erbrechen muss, wirkt der Blutverdünner schlechter	

Ich bin bei der Antwort sicher ☐Ja ☐Nein

9. Welches ist eine mögliche Nebenwirkung Ihres Blutverdünners?	
☐Blaue Flecken	☐Haarausfall
☐ Fusspilz	

Ich bin bei der Antwort sicher ☐Ja ☐Nein

10. Welches freiverkäufliche Schmerz- und Fiebermittel ist bei der Einnahme Ihres Blutverdünners am Sichersten?	
☐Acetylsalicylsäure (z.B. Aspirin®)	☐Paracetamol (z.B. Dafalgan®)
☐Ibuprofen (z.B. Algifor®)	

Ich bin bei der Antwort sicher ☐Ja ☐Nein

11. Sie möchten freiverkäufliche Medikamente einnehmen und wissen nicht, ob die Wirkung ihres Blutverdünners beeinflusst wird. Mit wem nehmen Sie am besten Rücksprache?	
☐BeimHerstellerdes Blutverdünners	☐ Beim Arzt / Apotheker
☐ Bei Freunden / Familie	

Ich bin bei der Antwort sicher ☐Ja ☐Nein

12. In welcher Situation sollten Sie Ihren Arzt informieren, dass Sie einen Blutverdünner einnehmen?	
☐Vor geplanten Operationen (inkl. Eingriffen beim Zahnarzt)	☐Vor einer Röntgenuntersuchung
☐ Vor einer Blutdruckmessung	

Ich bin bei der Antwort sicher ☐Ja ☐Nein

13. In welchen Situationen sollten Sie noch am selben Tag Ihre/n Ärztin/Arzt kontaktieren oder den Notfall aufsuchen?	
☐Bei Husten mit blutigem Auswurf	☐ Bei einer schmerzhaften Schürfwunde
☐ Bei Übelkeit und Brechreiz	

Ich bin bei der Antwort sicher ☐Ja ☐Nein

14. Wie oft sollten Sie sich aufgrund Ihres Blutverdünners für Kontrolluntersuchungen bei Ihrer/m Ärztin/Arzt melden?	
☐Alle 1-2 Wochen	☐ Mindestens 1 mal im Jahr
☐ Alle 1-2 Monate	

Ich bin bei der Antwort sicher ☐Ja ☐Nein

15. Was sollten Sie immer bei sich tragen, wenn Sie einen Blutverdünner einnehmen?	
☐Verbandsmaterial	☐ Blutverdünner-Ausweis
☐Blutspende-Ausweis	

Ich bin bei der Antwort sicher ☐Ja ☐Nein

Vielen Dank fürs Ausfüllen !

Universität Basel
Departement Pharmazeutische Wissenschaften
Pharmaceutical Care Research Group PCRG
Klingelbergstrasse 50, CH-4056 Basel (Schweiz)
DEPARTMENT OF PHARMACEUTICAL SCIENCES

Antwortkatalog zu Patientenfragebogen zu neuen oralen Gerinnungshemmern

Vorgehensweise:

1. Den beantworteten Fragebogen mit dem Patienten von Anfang bis Ende durchgehen
2. Bei nicht korrekt beantworteter Frage oder ‚Unsicherheit bei der Antwort' die Wissenslücke mit Hilfe dieses Antwortkatalogs und in einfacher Sprache füllen
3. Nachfragen ob die Information verstanden wurden mit: ‚Haben Sie alles verstanden oder möchten Sie dazu noch etwas wissen?'
4. Die Schritte 2. und 3. bei jeder nicht korrekt beantworteten Frage anwenden
5. Nachdem alle Fragen durchgegangen wurde, nachfragen: ‚Haben Sie noch weitere Fragen?'

Frage 1: Wie heisst Ihr Gerinnungshemmer?
• Eliquis® (Apixaban): Inhibitor Faktor Xa[1] • Xarelto® (Rivaroxaban): Inhibitor Faktor Xa[2] • Lixiana® (Edoxaban): Inhibitor Faktor Xa[3] • Pradaxa® (Dabigatran): Thrombininhibitor[4]

Frage 2: Wie lange müssen Sie Ihren Gerinnungshemmer einnehmen?
Indikation Vorhofflimmern: Die Therapie sollte solange fortgesetzt werden, wie das Risiko eines Schlaganfalls besteht. Dies kann eine lebenslange Einnahme zur Folge haben.[1-4] **Indikation TVT/Lungenembolie:** Nach einem Ereignis beträgt die empfohlene Dauer einer Therapie mindestens 3 Monate, sollte aber solange fortgesetzt werden, wie das Risiko eines Ereignisses besteht. Dies kann eine lebenslange Einnahme zur Folge haben.[1-4]

Frage 3: Wie oft täglich sollten Sie Ihren Gerinnungshemmer einnehmen?
Bei der **Schlaganfallsprophylaxe** wird die Dosierung nach Medikament unterschieden: ○ Xarelto®, Lixiana®: 1 mal täglich **oder** ○ Pradaxa®, Eliquis®: 2 mal täglich [1-4 7] Zur **Prophylaxe von Lungenembolien** und tiefen Venenthrombosen wird die Dosierung nach Medikament unterschieden: ○ Xarelto®, Lixiana®: 1 mal täglich **oder** ○ Pradaxa®, Eliquis®: 2 mal täglich Zur **Therapie von Lungenembolie oder tiefer Venenthrombose** wird die Dosierung ebenfalls nach Medikament unterschieden: ○ Lixiana®: 1 mal täglich **oder** ○ Pradaxa®, Eliquis®: 2 mal täglich **oder** ○ Xarelto®: während 3 Wochen 2 mal täglich eine tiefere Dosis (15mg), anschliessend nur noch 1 mal täglich eine höhere Dosis (20mg) [1-4]

Frage 4: Wozu wird Ihr Gerinnungshemmer eingesetzt wird?
Indikation Vorrhofflimmern: Der Gerinnungshemmer wird eingesetzt, um bei **Vorhofflimmern** die Bildung eines Blutgerinnsels zu verhindern und somit vor einem Schlaganfall zu schützen. [1-5] Wenn zusätzliche Information zu Vorhofflimmern erwünscht: Vorhofflimmern ist ein unregelmässiger Herzschlag und als Folge davon verliert das Herz an Pumpkraft. Die verminderte Pumpkraft des Herzens kann dazu führen, dass sich in den Herzvorhöfen Blutgerinnsel bilden, welche zu einem Schlaganfall führen können.[6] **Indikation TVT/Lungenembolie:** Der Gerinnungshemmer schützt Sie vor der Bildung eines Thrombus (Blutgerinnsels) und wird daher zur **Prophylaxe und Behandlung von tiefen Venenthrombosen und Lungenembolien** verwendet.[1-4] Wenn zusätzliche Information zu Thrombose/Lungenembolie erwünscht: Eine

Thrombose/Lungenembolie ist der Verschluss eines Blutgefässes durch ein Blutgerinnsel in den Beinen oder der Lunge. Als Folge davon tritt lokal eine Minderdurchblutung auf, welche schwerwiegende Folgen haben kann.[6]

Frage 5: Wie sollten Sie vorgehen, wenn Sie unsicher sind, ob Sie eine Tablette schon eingenommen haben?

- Bei 2 mal täglicher Dosierung: keine Tablette einnehmen und mit der nächsten regulären Dosis fortfahren.
- Bei 1 mal täglicher Dosierung und hohem Schlaganfallsrisiko: eine Tablette einnehmen und am nächsten Tag mit regulärer Dosis fortfahren.
- (Bei 1 mal täglicher Dosierung und tiefem Schlaganfallsrisiko: keine Tablette einnehmen und am nächsten Tag mit regulärer Dosis fortfahren).[8]

Frage 6: Wie sollten Sie vorgehen, wenn Sie vergessen haben eine Dosis einzunehmen?

Das Auslassen einer Dosis kann die Wirkung des Gerinnungshemmers beeinflussen, da das Medikament relativ schnell aus dem Körper eliminiert wird.[9]

- Bei 1 mal täglicher Dosierung: innerhalb von 12 Stunden sollte die vergessene Dosis nachgeholt werden. Wenn dies nicht mehr möglich ist, sollte die Dosis weggelassen und mit der nächsten regulären Dosis fortgefahren werden.
- Bei 2 mal täglicher Dosierung: innerhalb von 6 Stunden sollte die vergessene Dosis nachgeholt werden, bei erhöhtem Schlaganfallrisiko ist es jedoch empfohlen auf 12 Stunden zu erweitern und allenfalls zwei Tabletten gleichzeitig einzunehmen.[8]

Bei allen Gerinnungshemmern hält die Wirkung nach Absetzen 1-2 Tage an.[8]

Frage 7: Wie sollten Sie vorgehen, wenn Sie aus Versehen doppelt so viele Tabletten/Kapseln eingenommen haben?
• Bei 1 mal täglicher Dosierung: keine Dosis muss ausgelassen werden und es kann am nächsten Tag wie gewohnt mit der Einnahme fortgefahren werden. • Bei 2 mal täglicher Dosierung: die nächste Dosis sollte ausgelassen werden. Falls mehr als doppelt so viele Tabletten eingenommen wurden, sollte der Arzt kontaktiert werden, da gefährliche Blutungen auftreten können.[8]

Frage 8: Welcher Vorfall kann die Wirkung Ihres Gerinnungshemmers wesentlich beeinflussen?
Erbrechen innerhalb von 2-4 Stunden nach der Einnahme kann die Wirkung des Gerinnungshemmers wesentlich beeinflussen, da es zu einer verminderten Aufnahme des Gerinnungshemmers in den Körper führen kann und dadurch die Gerinnungshemmung vermindert ist.

Frage 9: Welches ist eine mögliche Nebenwirkung Ihres Gerinnungshemmers?
Blaue Flecken sind eine mögliche Nebenwirkung. Zusätzlich gibt es weitere Nebenwirkungen wie Nasenbluten, Zahlfleischbluten, Übelkeit, Erbrechen, Durchfall, Fieber, Schwindel, Kopfschmerzen, Anämie, Kraftlosigkeit, Müdigkeit sowie Jucken der Haut und Hautausschlag die auftreten können.[2 4] Achtung: Kleinere Blutungen wie grossflächig auftretende blaue Flecken oder Nasenbluten länger als 10 Minuten sind nicht mehr nur eine Nebenwirkung sondern sollten der/dem behandelnden Ärztin/Arzt gemeldet werden.[9 10]

Frage 10: Welches freiverkäufliche Schmerz- und Fiebermittel ist bei der Einnahme Ihres Gerinnungshemmers am Sichersten?
Paracetamol ist bei Einnahme eines Gerinnungshemmers das Sicherste freiverkäufliche Schmerz- und Fiebermittel. Bei ASS sowie NSAR ist das Blutungsrisiko erhöht.[1-4]

Frage 11: Einige freiverkäufliche Medikamente können die Wirkung Ihres Gerinnungshemmers beeinflussen. Bei wem nehmen Sie vor deren Einnahme Rücksprache?
Es empfiehlt sich, zuerst in der Apotheke oder bei der/dem behandelnden Ärztin/Arzt nachzufragen, ob sich das Medikament mit dem Gerinnungshemmer verträgt, da auch rezeptfreie Medikamente die Wirkung des Gerinnungshemmers beeinflussen können. [8] [10]

Frage 12: In welchen Situationen sollten Sie die/den Ärztin/Arzt darauf hinweisen, dass Sie einen Gerinnungshemmer einnehmen?
Bei einer geplanten Operation besteht ein erhöhtes Blutungsrisiko, deshalb muss hier die/der Ärztin/Arzt zwingend darauf hingewiesen werden, dass ein Gerinnungshemmer eingenommen wird. Beim Zahnarztbesuch kann je nach Eingriff ein geringes aber auch ein erhöhtes Blutungsrisiko bestehen, daher zur Sicherheit auch hier darauf hinweisen.[11] Zudem sollte bei einer Behandlung durch eine/n neue/n Ärztin/Arzt darauf hingewiesen werden. Diese/r könnte ein Medikament verschreiben, welches mit dem Gerinnungshemmer eine Wechselwirkung eingehen kann und es dadurch zu einer verstärkten oder abgeschwächten Wirkung kommt. Aus demselben Grund sollte auch die/der behandelnde Ärztin/Arzt über die Therapie eines anderen Arztes informiert werden.[8]

Frage 13: In welchen Situationen sollten Sie Ihre/n Ärztin/Arzt kontaktieren oder den Notfall aufsuchen?
Bei Husten mit blutigem Auswurf sollte die/der behandelnde Ärztin/Arzt kontaktiert werden, da es auf eine schwere Blutung hinweisen könnte. Falls diese/r nicht erreichbar ist, sollte der Notfall aufgesucht werden.[10]

Frage 14: Wie oft sollten Sie sich aufgrund Ihres Gerinnungshemmers für Kontrolluntersuchungen bei Ihrer/m Ärztin/Arzt melden?
Bei der Einnahme eines Gerinnungshemmers sollte alle 1-3 Monate die/der behandelnde Ärztin/Arzt konsultiert werden. Bei Langzeitanwendung sollte die Nierenfunktion in regelmässigen Abständen kontrolliert werden, um allfällige Dosisanpassungen des Gerinnungshemmers bei einer Verschlechterung der Nierenfunktion vorzunehmen. Ausserdem sollten die Blut- und Leberwerte jährlich kontrolliert werden.[8 11]

Frage 15: Was sollten Sie immer bei sich tragen, wenn Sie einen Gerinnungshemmer einnehmen?
Sobald ein Gerinnungshemmer eingenommen wird, sollte immer ein sogenannter Antikoagulations-Ausweis bei sich getragen werden. So kann in einem Notfall durch den Notfallarzt oder das Spital schnell festgestellt werden, dass ein Gerinnungshemmer eingenommen wird. Dadurch kann viel wertvolle Zeit gespart werden, die für die lebensrettende Behandlung verwendet werden kann. Zudem kann der Ausweis auch beim Zahnarzt, bei einer/m neuen Ärztin/Arzt oder in der Apotheke vorgewiesen werden, um zu zeigen, dass ein Gerinnungshemmer eingenommen wird.[6]

Referenzen

1. Kompendium. Fachinformation Eliquis des Arzneimittel-Kompendium der Schweiz 09.04.2015 [Available from: https://compendium.ch/mpro/mnr/22732/html/de.
2. Kompendium. Fachinformation Xarelto des Arzneimittel-Kompendium Schweiz 18.12.2015 [Available from: https://compendium.ch/mpro/mnr/20753/html/de.
3. Kompendium. Fachinformation Lixiana des Arzneimittel-Kompendium der Schweiz 05.05.2015 [Available from: https://compendium.ch/mpro/mnr/26503/html/de.
4. Kompendium. Fachinformation Pradaxa des Arzneimittel-Kompendium der Schweiz 07.10.2015 [Available from: https://compendium.ch/mpro/mnr/23436/html/de.
5. Bayer. *Quick Guide Xarelto Across Indications*, 01.2014.
6. Bayer. *Patientenbroschüre für Xarelto: Schlaganfallprophylaxe bei Vorhofflimmern*.
7. Corina Metaxas dp. Rivaroxaban (Xarelto®) – Indikationserweiterung & Management. im@il offizin 15.07.2015.
8. Heidbuchel H, Verhamme P, Alings M, et al. Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology 2015;**17**(10):1467-507.
9. Bayer. *Anwendungskarte Xarelto (Rivaroxaban)*.
10. Lane DA, Wood K. Cardiology patient page. Patient guide for taking the non-vitamin K antagonist oral anticoagulants for atrial fibrillation. Circulation 2015;**131**(16):e412-5.
11. Wuillemin WA, et al., . Fragen und Antworten zum Einsatz von Rivaroxaban (Xarelto) in der Praxis. 2013.

UNIVERSITÄT BASEL

DEPARTMENT OF PHARMACEUTICAL SCIENCES

Rückmeldeformular zur Umfrage: Testversion des Fragebogens „Was wissen Patienten/Patientinnen über Ihren Blutverdünner?"

Bitte nehmen Sie zu folgenden Aussagen Stellung (mit Note und Kommentaren bei Vergabe von Note 1 oder 2). Gerne dürfen Sie Kommentare auch direkt im Fragebogen notieren.
Vielen Dank für Ihre wertvolle Rückmeldung!

Notenskala: 1 = trifft nicht zu, 2 = trifft eher nicht zu, 3 = trifft eher zu, 4 = trifft zu

1. Die **Handhabung des Fragebogens** war klar und logisch aufgebaut	Note: ____	Kommentar:_____ _____
2. Die Fragen sind **allgemein verständlich** formuliert	Note: ____	Kommentar:_____ _____
3. Die Fragen sind **präzise** formuliert	Note: ____	Kommentar:_____ _____
4. Die **Antwortskalen** zu den Fragen haben mir alle Optionen für meine Angaben ermöglicht	Note: ____	Kommentar:_____ _____
5. Das Schriftbild ist **gut lesbar**	Note: ____	Kommentar:_____ _____
6. Die **Zeitangabe von 10 Minuten** zum Ausfüllen des Fragebogens ist angemessen	Note: ____	Kommentar:_____ _____

Universität Basel
Departement Pharmazeutische Wissenschaften
Pharmaceutical Care Research Group PCRG
Klingelbergstrasse 50, CH-4056 Basel (Schweiz)
DEPARTMENT OF PHARMACEUTICAL SCIENCES

Patientenfragebogen zur Therapie mit Blutverdünnern

Vielen Dank, dass Sie sich dazu bereit erklärt haben, an unserer Befragung teilzunehmen. Bitte füllen Sie diesen Fragebogen. Das Ausfüllen dauert ungefähr 5 Minuten. Bei Unklarheiten, dürfen Sie sich gerne an den/die ApothekerIn wenden.

Fragen zu Ihrer Therapie mit dem Blutverdünner

		Stimme überhaupt nicht zu	Stimme eher nicht zu	Weder noch	Stimme eher zu	Stimme voll und ganz zu
1.	Ich bin **überzeugt** davon, dass ich meinen Blutverdünner **benötige.**	O	O	O	O	O
2.	Ich bin **überzeugt** davon, dass mein Blutverdünner **mir hilft.**	O	O	O	O	O
3.	Ich habe **Vertrauen** in meinen Blutverdünner.	O	O	O	O	O
4.	Ich fühle mich **sicher** bei der Anwendung meines Blutverdünners.	O	O	O	O	O
5.	Ich **mache mir Sorgen** wegen der Nebenwirkungen meines Blutverdünners.	O	O	O	O	O

		Nie	Fast nie	Manchmal	Häufig	Sehr häufig
6.	Ich **vergesse** meinen Blutverdünner einzunehmen.	O	O	O	O	O

7.	Seit wann nehmen Sie Ihren Blutverdünner ein?	_____(Z.B.: seit 2005)			
8.	Wie schätzen Sie Ihr Wissen über Blutverdünner ein?	O Hervorragend	O Gut	O Mässig	O Schlecht

Fragen zur Person			
9.	Geschlecht:	O Frau	O Mann
10.	Wann sind Sie geboren?	_____(Z.B.: 10. Mai 1987)	
11.	Bitte geben Sie die höchste Ausbildung an, die Sie abgeschlossen haben	O obligatorische Schulzeit O Berufslehre / Berufsschule O höhere Berufsausbildung (z.B. Meister, o.ä.) O Matura O Fachhochschule O Universität O keine Angabe	
12.	Wie viele **vom Arzt** verschriebene Medikamente nehmen Sie täglich ein?	O 1-3 verschiedene Medikamente O 4-10 verschiedene Medikamente O mehr als 10 verschiedene Medikamente	
13.	Verwenden Sie eine Medikamentenbox, um Ihre Medikamente bereitzustellen? (Zum Beispiel: Dosett®)	O Ja Welches:_____	O Nein

		Sehr sicher	Ziemlich sicher	Einiger-massen sicher	Wenig sicher	Überhaupt nicht sicher
14.	Wie sicher sind Sie beim selbstständigen Ausfüllen von Formularen?	O	O	O	O	O

		Stimme überhaupt nicht zu	Stimme eher nicht zu	Weder noch	Stimme eher zu	Stimme voll und ganz zu
15.	**Schriftliche Informationen** über Medikamente sind schwierig zu verstehen.	O	O	O	O	O
16.	**Mündliche Informationen** über Medikamente sind schwierig zu verstehen.	O	O	O	O	O

Besten Dank für das Ausfüllen!

UNIVERSITÄT BASEL

Departement Pharmazeutische Wissenschaften
Pharmaceutical Care Research Group

Klingelbergstrasse 50
CH-4056 Basel

Studienkoordination
Tel. +41 (0)61 267 15 29

Abschliessende Fragen zur Studie neue Blutverdünner

Während er Befragungsstudie haben Sie von ihrem Apotheker/ ihrer Apothekerin gezielte Informationen über Ihren Blutverdünner erhalten. Gerne möchten wir Ihre Eindrücke und Erfahrungen zu dieser Schulung auswerten. Bitte beantworten Sie dazu diese 9 Fragen.

Seit dem Gespräch mit dem Apotheker...

		Stimme überhaupt nicht zu	Stimme eher nicht zu	Weder noch	Stimme eher zu	Stimme voll und ganz zu
1.	… **weiss ich mehr** über meinen Blutverdünner	O	O	O	O	O
2.	…bin ich **überzeugter** davon, dass ich **meinen Blutverdünner benötige**	O	O	O	O	O
3.	…habe ich **weniger Bedenken,** dass mein Blutverdünner mir **nicht** hilft.	O	O	O	O	O
4.	…habe ich **mehr Vertrauen** in meinen Blutverdünner	O	O	O	O	O
5.	…fühle ich mich **sicherer** in der Anwendung mit meinem Blutverdünner	O	O	O	O	O
6.	…mache ich mir **weniger Sorgen** wegen der Nebenwirkungen meines Blutverdünners	O	O	O	O	O
7.	…**vergesse ich seltener** meinen Blutverdünner einzunehmen.	O	O	O	O	O
8.	Der/die Apotheker/in konnte **meine Fragen** zu meiner Zufriedenheit	O	O	O	O	O
9.	Ich würde diese Dienstleistung weiter empfehlen	O	O	O	O	O

Datum _____

UNIVERSITÄT BASEL

Departement Pharmazeutische Wissenschaften
Pharmaceutical Care Research Group

Klingelbergstrasse 50
CH-4056 Basel

Studienkoordination
Tel.+41 (0)61 267 15 29

Weitere Kommentare:

Beschlussmitteilung der Ethikkommission Nordwest- und Zentralschweiz

Die Ethikkommission Nordwest- und Zentralschweiz (bis 31.12.13 EKBB) hat das nachstehende Forschungsprojekt anlässlich der Sitzung vom 13. Februar 2014 (in der Zusammensetzung, wie sie auf Seite 2 wiedergegeben ist) nochmals eingehend begutachtet.

Titel des Forschungsprojektes Ref.Nr. **EKBB: 338/13**

Adequacy of Serum vitamin B_{12} measurement in Type 2 diabetic patients treated with Metformin in comparison to Holotranscobalamin measurement

Prüfer/in

Name, Vorname, Titel:	Hersberger, Kurt E., Prof. Dr.
Funktion:	Studienleitung Dept. Pharmazeutische Wissenschaften
Adresse:	Klingelbergstrasse 50, 4056 Basel

Die Ethikkommission stützt ihre Beurteilung auf die Unterlagen, wie sie in den beiliegenden "Anträgen auf Begutachtung" vom 01. Dezember 2013 abschliessend aufgezählt sind.

X normales Verfahren ☐ vereinfachtes Verfahren ☐ Nachbegutachtung

Die Ethikkommission kommt zu folgendem **Beschluss**:

X A positiv
☐ **B positiv mit Bemerkungen** (siehe Seite 2ff)
☐ **C mit Auflagen** (siehe Seite 2ff)
Nachbegutachtung durch Ethikkommission notwendig ☐
schriftliche Mitteilung an Ethikkommission ausreichend ☐
☐ **D negativ (mit Begründung und Erläuterung für die Neubeurteilung)** (siehe Seite 2ff)
☐ **E Nicht-Eintreten (mit Begründung)** (siehe Seite 2ff)

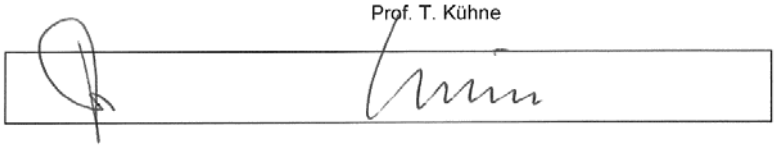
Der Beschluss gilt auch für die im "Antrag auf Begutachtung" gemeldeten weiteren Prüfer/innen im Zuständigkeitsbereich der Ethikkommission.

Pro Memoria: **Pflichten des/der verantwortlichen Prüfers/in**
- Geprüfte Produkte und Vergleichsprodukte (Arzneimittel und Medizinalprodukte) müssen - zur Sicherstellung der Qualität und der Sicherheit - fachgerecht hergestellt, evaluiert und eingesetzt werden.
- Meldepflicht bei:
  a) schwerwiegenden unerwünschten Ereignissen (serious adverse events) unverzüglich
  b) neuen Erkenntnissen, die während des Versuchs verfügbar werden und die Sicherheit der Versuchspersonen sowie die Weiterführung des Versuchs beeinflussen können
  c) Änderung des Protokolls (Versuchsplans)
  d) Ende oder Abbruch der Studie
- Zwischenbericht: einmal pro Jahr
- Meldungs- oder Bewilligungspflicht von Studien bei Swissmedic bzw. anderen Bundes- oder kantonalen Behörden - sofern erforderlich (bei sponsorisierten Studien ist dies die Pflicht des Sponsors)
- Schlussbericht

Für die Ethikkommission:

Ort, Datum: Basel, 18. Februar 2014 Name(n): Prof. A. P. Perruchoud
Prof. T. Kühne

Unterschrift(en):



Ref. Nr. 338/13

Zusammensetzung der Ethikkommission

Die Ethikkommission tagte in der nachfolgend erwähnten Zusammensetzung und war damit beschlussfähig (Art. 32 der Verordnung über klinische Versuche mit Heilmitteln vom 17. 10. 2001)

					am Beschluss beteiligt	
	Name, Vorname	**Berufliche Stellung / Titel**	**m**	**f**	**ja**	**nein**
Vorsitz	Prof. A. P. Perruchoud	Präsident der EKNZ	X	☐	X	☐
Mitglieder	Fr. Dr. B. Kuhlmann	FMH Kinder- und Jugendmedizin, Aarau	☐	X	X	☐
	Fr. PD Dr. M. Thumshirn	Chefärztin, St. Claraspital	☐	X	X	☐
	Prof. T. Girard	FMH Anästhesie, US Basel	X	☐	X	☐
	Frau E. Seeberger	Study Nurse, Dept. Anästhesie, USB	☐	X	X	☐
	Fr. Dr. O. Forrer	Theologin, Chemikerin, Basel & Aarau	☐	X	X	☐
	Fr. lic. iur. P. Estermann	Nationale Suisse, Luzern	☐	X	X	☐
	Dr. T. Gruberski	Jurist, Rechtsdienst, USB	X	☐	X	☐
für Biometrie zuständiges Mitglied	PD Dr. M. Koller	Klinische Epidemiologie, USB	X	☐	X	☐

Auflagen:

- **Die initialen Auflagen der EKBB (siehe Schreiben vom 20. Dezember 2013) wurden erfüllt.**

Bemerkungen

- **Die EKNZ hat die nachfolgend erwähnten Dokumente zur oben genannten Studie zustimmend zur Kenntnis genommen und genehmigt:**
  - **Studienprotokoll - Version 2 vom 30. Januar 2014**
  - **Zusammenfassung des Studienprotokolls - Version 2 vom 30. Januar 2014**
  - **Patienteninformation - Version 2 vom 22. Januar 2014**
  - **Einverständniserklärung - Version vom 13. Januar 2014**
  - **Patienten-Fragebogen**
  - **Vereinbarung (Prof. Rudofsky, Dr. Walter)**
  - **CV (Dr. Walter, inkl. CGP-Nachweis & GCP-Nachweis Fr. Metaxas).**
- **Die EKNZ bestätigt, dass sie nach GCP-ICH-Richtlinien arbeitet**

(erweiterbar)

CRF	Prüfer Initialen	Datum (TT/MM/JJ)	Patient Code
	☐☐	☐☐☐☐☐☐	☐☐☐☐

Case Report Form (CRF)

Studie	**Metformin/ VB12 Biomarker Studie**
Studienregister	**ClinicalTrials.gov Nr. NCT02111967**
Studienzentrum	Kantonsspital Olten Baslerstrasse 150 4600 Olten
Principal Investigator	Dr. Philipp Walter, Pharmaceutical Care Research Group der Universität Basel, Klingelbergstrasse 50, 4058 Basel

Auszufüllen durch Mitarbeitende des Studienteams.

1 Patienten Basisinformation

Ziffer			JA	NEIN
1.1	Patienten-Code	V/K - ☐☐☐☐	☐	☐
1.2	Geschlecht	☐männlich ☐weiblich	☐	☐
1.3	Geburtsjahr	☐☐☐☐ (JJJJ)	☐	☐
1.4	Einverständnis-erklärung	Liegt die unterschriebene Einverständniserklärung für die Studienteilnahme vor? (☞ falls NEIN: keine Studienteilnahme)	☐	☐
1.5	Rekrutierender Arzt	NAME Arzt ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐	☐	☐

2 Einschluss- und Ausschlusskriterien

Ziffer			JA	NEIN
Einschlusskriterien		(Einschluss, falls alle Fragen mit JA beantwortet)		
2.1	Alter	Patient-/in ist mindestens 18 Jahre alt	☐	☐
2.2	Diagnose	Es liegt die ärztliche Diagnose Diabetes mellitus Typ 1 oder 2 vor	☐	☐
		Der Patient leidet an Diabetes mellitus Typ 1 ☐ Typ 2 ☐		
2.3.	Einverständnis-erklärung	Der Patient hat den Ablauf der Studie verstanden, wurde über die Folgen einer Studienteilnahme informiert und hat freiwillig sein Einverständnis zur Studienteilnahme gegeben.	☐	☐
2.4	Nur für Versuchsgruppe:	Der Patient nimmt seit mindestens 6 Monaten Metformin ein	☐	☐
2.5	Nur für Kontrollgruppe:	Der Patient nimmt kein Metformin ein	☐	☐
Ausschlusskriterien		(Ausschluss, falls mind. 1 Frage mit JA beantwortet)		
2.6.	Konsum von VB12 Präparaten	Der Patient hat innerhalb der Studienteilnahme vorangehenden 3 Monaten pharmazeutische Präparate konsumiert, welche Einfluss auf die Vitamin B_{12} Versorgungslage haben können.	☐	☐
2.7.	Sprachliche Verständigung	Mit dem Patienten / der Patientin ist keine ausreichende Verständigungsmöglichkeit auf Deutsch, Französisch, Italienisch oder Englisch möglich	☐	☐
2.8	Diagnosen	Der Patient hat mindestens eine der folgender Diagnosen. • *Transcobolamin Transporter Defekt* • *Leberinsuffizienz im Stadium B oder C (nach Child-Pugh Scores)* ***oder*** *akute Hepatitis* *Niereninsuffizienz ab Stadium III (nach KDOQI)* ***oder*** *akute Nierenfunktionsstörung*	☐	☐

CRF	Prüfer Initialen	Datum (TT/MM/JJ)	Patient Code
	☐☐	☐☐☐☐☐☐	☐☐☐☐

3 Fragebogen Q- Demographie , Co-Medikation und Ernährung

- Quelldokument **Q-DCN**

Ziffer		JA	NEIN
3.1	Ist der Fragebogen Q-DCN vollständig ausgefüllt vom Patienten zurückerhalten worden?	☐	☐

4 Visit T1 beim Diabetologen

*Die Daten werden beim Diabetologen durch Praxismitarbeiter, welche durch den Studienleiter entsprechend geschult wurden, erfasst. Die Daten werden auf einem nicht anonymisierten Quelldokument (**F-T1**) erfasst und an das Studienzentrum übermittelt. Die Übertragung der Daten in das CRF erfolgt durch Mitarbeitende des Studienzentrums.*

Ziffer		**JA**	**NEIN**
4.1	Datum des Visits ☐☐/☐☐/☐☐ (TT/MM/JJ) ☐☐:☐☐ (HH:MM)		
4.2	Die Voraussetzungen für eine Studienteilnahme gemäss Ziff. 1 und 2 sind gegeben	☐	☐
4.3	Die Blutprobe konnte entnommen werden:	☐	☐
	Datum: ☐☐/☐☐/☐☐ (TT/MM/JJ) *Zeit:* ☐☐:☐☐ (HH:MM)	☐	☐
4.4	Bestätigung des ausführenden Mitarbeiters, dass die Schritte in Ziff. 4.1 bis 4.10. wie vorgesehen durchgeführt liegt vor?	☐	☐

5 Laborresultate

Die Laborresultate des Besuchs T1 sind als Befundausdrucke dem CRF beizulegen (F-Lab).

Ziffer		JA	NEIN
5.1	Sind die Laborresultate vollständig vorhanden?	☐	☐
5.2	Ist die korrespondierenden Proben in der Studienserothek vorhanden.	☐	☐

CRF	Prüfer Initialen	Datum (TT/MM/JJ)	Patient Code

Checklist Quelldokumente

Bitte prüfen Sie bei Abschluss der Studienteilnahne, ob alle unten aufgeführten Quelldokumente vorhanden und vollständig ausgefüllt sind.
A = Anonymisiert
P = Personalisiert
SZ = Auszufüllen durch Studienmitarbeiter

	Code	Typ	Bezeichnung	A/P	Auszufüllen durch:	Vollständig? Visum
1	F-IC	Formular	Unterzeichnete Einverständniserklärung	P	Patient +SZ	
2	Q-DCN	Fragebogen	Demographie, Co-Medikation und Ernährung	A	Patient	
3	F-T1	Formular	Dokumentation T1 (Arztpraxis)	P	Praxis	
4	F-LAB	Formular	Laborresultate T1	A	SZ	

solothurner spitäler ag

Departement Pharmazeutische Wissenschaften
Pharmaceutical Care Research Group
Tel. 061 267 15 19
Fax 061 267 15 28
corina.metaxas@unibas.ch

UNI

Einverständniserklärung zur Studienteilnahme

Vitamin B_{12} Studie

- Bitte lesen Sie dieses Formular sorgfältig durch.
- Bitte fragen Sie, wenn Sie etwas nicht verstehen oder wissen möchten.

Nummer der Studie:	
Titel der Studie:	Biomarkerstudie: Bestimmung des Vitamin B_{12} Status
Sponsor :	Pharmaceutical Care Research Group der Universität Basel, Klingelbergstrasse 50, 4058 Basel
Ort der Studie:	Kantonsspital Olten ; Olten
Prüfer: Name und Vorname:	Prof. Dr med. Rudofsky, Kantonsspital Olten; Baslerstrasse 150 4600 Olten
Patientin/Patient Geburtsdatum: Name und Vorname: Adresse: Telefon Nummer:	☐ männlich ☐ weiblich
Studienidentifikationsnummer: (Wird durch einen Studienmitarbeiter ausgefüllt)	

- Ich wurde vom unterzeichnenden Prüfer mündlich und schriftlich über die Ziele, den Ablauf der Studie, über die zu erwartenden Wirkungen, über mögliche Vor- und Nachteile sowie über eventuelle Risiken informiert.
- Ich habe die zur oben genannten Studie abgegebene schriftliche PatientInneninformation gelesen und verstanden. Meine Fragen im Zusammenhang mit der Teilnahme an dieser Studie sind mir zufriedenstellend beantwortet worden. Ich kann die schriftliche Patientinneninformation behalten und erhalte eine Kopie meiner schriftlichen Einverständniserklärung.
- Ich hatte genügend Zeit, um meine Entscheidung zu treffen.
- Ich weiss, dass meine persönlichen Daten nur in anonymisierter Form an aussenstehende Institutionen zu Forschungszwecken weitergegeben werden. Ich bin einverstanden, dass die zuständigen Fachleute Studienauftraggebers, der Behörden und) der Kantonalen Ethikkommission zu Prüf- und Kontrollzwecken in meine Originaldaten Einsicht nehmen dürfen, jedoch unter strikter Einhaltung der Vertraulichkeit.
- Ich nehme an dieser Studie freiwillig teil. Ich kann jederzeit und ohne Angabe von Gründen meine Zustimmung zur Teilnahme widerrufen, ohne dass mir deswegen Nachteile bei der weiteren medizinischen Betreuung entstehen. In diesem Fall werde ich zu meiner Sicherheit abschliessend medizinisch untersucht.
- Im Interesse meiner Gesundheit kann mich der Prüfer jederzeit von der Studie ausschliessen. Zudem orientiere ich den Prüfer über die gleichzeitige Behandlung bei einem anderen Arzt sowie über die Einnahme von Medikamenten (vom Arzt verordnete oder selbständig gekaufte).

Ort, Datum	Unterschrift der Patientin/des Patienten

Bestätigung des Prüfers: Hiermit bestätige ich, dass ich diesem Patienten/dieser Patientin Wesen, Bedeutung und Tragweite der Studie erläutert habe. Ich versichere, alle im Zusammenhang mit dieser Studie stehenden Verpflichtungen zu erfüllen. Sollte ich zu irgendeinem Zeitpunkt während der Durchführung der Studie von Aspekten erfahren, welche die Bereitschaft der Patientin/des Patienten zur Teilnahme an der Studie beeinflussen könnten, werde ich sie/ihn umgehend darüber informieren.

Ort, Datum	Unterschrift der Prüfers

Vitamin B_{12} Studie	Routinekonsultation Patienten mit Diabetes mellitus	Prüfer Initialen	Patient Initialen	Patient JG
		☐☐	☐☐	☐☐

Dokumentation Arztpraxis

1. Einschlusskriterien

		ja	nein
1.1	**Datum** des Besuchs : ☐☐ ☐☐ ☐☐ (TT/MM/JJ) **Uhrzeit**: ☐☐ ☐☐ (HH:MM)		
1.2	Die Diagnose **Diabetes mellitus (Typ 1 oder 2)** ist seit mindestens 6 Monaten bekannt.	☐	☐
	Der Patient leidet an Diabetes mellitus **Typ 1** ☐ **Typ 2** ☐		
1.3	**Gilt nur für die Metformin-Gruppe:** Die Metformin-Therapie wird seit mehr als 6 Monaten durchgeführt.	☐	☐
1.4	**Gilt nur für die Kontroll-Gruppe:** Der Patient nimmt **kein** Metformin ein.	☐	☐
1.5	Ist die sprachliche Verständigungsmöglichkeit für die Studienteilnahme ausreichend?	☐	☐
1.6	Patient/-in ist mindestens 18 Jahre alt?	☐	☐
1.7	Der Patient hat im vorangehenden Monat **keine** pharmazeutischen Präparate konsumiert, welche Einfluss auf die Vitamin B_{12} - Versorgung haben.	☐	☐
1.8	Der Patient hat **keine** bestehende Diagnose folgender Krankheiten: • Transcobolamin Transporter Defekt • Leberinsuffizienz im Stadium B oder C (nach Child-Pugh Scores) **oder** akute Hepatitis • Niereninsuffizienz ab Stadium III (nach KDOQI) **oder** akute Nierenfunktionsstörung	☐ ☐ ☐	☐ ☐ ☐
1.9	Liegt die unterzeichnete **Einverständniserklärung** (F-IC) vor? ☞ falls 'nein' → Bitte Formular unterzeichnen lassen.	☐	☐
	Wurde der **Fragebogen** mit der beiliegenden Patienten-Information dem Patienten abgegeben? ☞ falls 'nein' → Bitte dem Patienten mitgeben.	☐	☐
Φ	Schritte 1.2 bis 1.9 stellen Einschlusskriterien dar. Ist eine der Fragen 1.2 bis 1.9 nicht mit 'ja' beantwortet, so kann der Patient **nicht** in die Studie aufgenommen werden.		

2. Blutentnahme

2.1	**Wann** wurde die Blutprobe entnommen? **Datum**: ☐☐ ☐☐ ☐☐ (TT/MM/JJ) **Zeit**: ☐☐ ☐☐ (HH:MM) **Visum**: _____

Bitte wenden →

	Routinekonsultation	Prüfer Initialen	Patient Initialen	Patient JG
Vitamin B_{12} Studie	*Patienten mit Diabetes mellitus*			

3. Neuropathie Defizit-Score (NDS)

3.1 Achillessehnenreflex		
Reflex:	**links**	**rechts**
normal	☐ 0	☐ 0
abgeschwächt	☐ 1	☐ 1
fehlend	☐ 2	☐ 2
3.2 Vibrationsempfindung		
Messung am Fussrücken: (1. Metatarsale distal)	**links**	**rechts**
normal (≥5/8)	☐ 0	☐ 0
abgeschwächt/fehlend (<5/8)	☐ 1	☐ 1
3.3 Schmerzempfindung		
Messung am Fussrücken:	**links**	**rechts**
normal	☐ 0	☐ 0
abgeschwächt/fehlend	☐ 1	☐ 1
3.4 Temperaturempfindung		
Messung am Fussrücken:	**links**	**rechts**
normal	☐ 0	☐ 0
abgeschwächt/fehlend	☐ 1	☐ 1
Gesamtscore:		

Bewertung: **3-5** = **leichte** neuropathische Defizite
6-8 = **mässige** neuropathische Defizite
9-10 = **schwere** neuropathische Defizite

Herzlichen Dank für Ihre wertvolle Mitarbeit.

DEPARTMENT
OF PHARMACEUTICAL SCIENCES

Dr. Philipp Walter
Institutsleiter Labormedizin

338/13

soH solothurner spitäler ag

062 311 48 19 / 062 311 54 86
philipp.walter@spital.so.ch

Patienten-Fragebogen

Herzlichen Dank, dass Sie sich entschieden haben, an dieser Studie teilzunehmen.

Dieser Fragebogen wurde speziell für **Diabetes-Patienten** entwickelt, um Risikofaktoren zu ermitteln, welche einen **Vitamin B_{12}-Mangel** auslösen können. Aus den Resultaten dieser Umfrage soll es in Zukunft möglich sein, einen Mangel frühzeitig zu erkennen.

Bitte versuchen Sie **alle** Fragen zu beantworten, damit Ihr Fragebogen vollständig ausgewertet werden kann. Bitte kreuzen Sie diejenigen Antworten an, welche auf Sie persönlich zutreffen. Es gibt keine richtigen oder falschen Antworten.
Ihre Angaben werden streng vertraulich und anonym behandelt. Wenn Sie den Fragebogen vollständig ausgefüllt haben, retournieren Sie diesen bitte **bis spätestens eine Woche nach Erhalt** im beiliegenden Antwortcouvert an unser Studienzentrum der Universität Basel.

Bitte zögern Sie nicht, uns **bei Fragen oder Unklarheiten** jederzeit zu kontaktieren. Wir beraten Sie gerne unter der Telefonnummer **078 835 25 99**.

Persönliche Angaben

Geburtsdatum: _____/_____/_____ (Tag/Monat/Jahr) **Initialen:** ☐☐

Körpergrösse (cm): _____ **Gewicht** (kg): _____

Geschlecht: O weiblich O männlich

1 Angaben zu Ihrem Gesundheitszustand

		ja	nein
a.	Haben Sie in den letzten drei Monaten an psychischem Stress oder an einer akuten Krankheit gelitten?	☐	☐
b.	Haben Sie Probleme mit Ihrem Geschmackssinn?	☐	☐
c.	Fühlen Sie sich oft müde und weniger leistungsfähig?	☐	☐
d.	Haben Sie in den letzten drei Monaten aufgrund von Appetitlosigkeit, Verdauungs- oder Schluckbeschwerden weniger Nahrung als üblich zu sich genommen?	☐	☐

		nein	weniger als 1 kg	zwischen 1-3 kg	mehr als 3 kg	nicht bekannt
e.	Haben Sie in den letzten drei Monaten **unfreiwillig** Gewicht verloren?	☐	☐	☐	☐	☐

2 Beschwerden an Fuss und Unterschenkel

		ja	nein
a.	Haben Sie in letzter Zeit folgende Anzeichen **an Füssen oder Unterschenkeln** bemerkt?		
I.	Brennen?	☐	☐
II.	Taubheitsgefühle (z.B.: das Gefühl von eingeschlafenen Beinen)?	☐	☐
III.	Missempfindungen (z.B.: Ameisenlaufen oder Kribbeln)?	☐	☐
IV.	Schwächegefühl (z.B.: Erschöpfung und Ermüdung)?	☐	☐
V.	Muskelkrämpfe?	☐	☐
VI.	Schmerzen? ☞ ***Wenn ‚ja':*** *Welche Schmerzmittel nehmen Sie dagegen ein?* _____	☐	☐
b.	**Wo** treten diese Anzeichen hauptsächlich auf? (nur **eine** Antwort möglich)	**ja**	**nein**
I.	an Füssen?	☐	☐
II.	an Unterschenkeln?	☐	☐
III.	an einem anderen Ort?	☐	☐
c.	**Wann** sind diese Anzeichen besonders stark?	**ja**	**nein**
I.	nachts?	☐	☐
II.	tagsüber und nachts?	☐	☐
III.	nur tagsüber?	☐	☐
IV.	Wurden Sie schon einmal durch diese Anzeichen aus dem Schlaf geweckt?	☐	☐
d.	**Bessern** sich diese Anzeichen beim.....? (nur **eine** Antwort möglich)	**ja**	**nein**
I.	Gehen?	☐	☐
II.	Stehen?	☐	☐
III.	Sitzen oder Hinlegen?	☐	☐

3 Fragen zu Ihrer Medikamenteneinnahme

		ja	nein
a.	Leiden Sie an depressiven Verstimmungen oder an einer Depression?	☐	☐
I.	Nehmen Sie Medikamente zur Stimmungsaufhellung (Antidepressiva) ein?	☐	☐
II.	☞ ***Wenn ‚ja':*** *Welche?* _____		
b.	Macht es Ihnen Mühe, sich an Ereignisse zu erinnern, die kurze Zeit zurückliegen (z.B.: Besuche oder Ausflüge)?	☐	☐
I.	Nehmen Sie Medikamente ein, welche die Gedächtnisleistung unterstützen?	☐	☐
II.	☞ ***Wenn ‚ja':*** *Welche?* _____		
c.	Leiden Sie häufig unter Magenschmerzen oder Sodbrennen?	☐	☐
I.	Nehmen Sie **regelmässig** Medikamente dagegen ein?	☐	☐
II.	☞ ***Wenn ‚ja':*** *Welche?* _____		
d.	Wurde bei Ihnen bereits eine Vitamin B_{12} – Therapie durchgeführt?	☐	☐
I.	☞ ***Wenn ‚ja':*** *Wurde diese Therapie mit einer Spritze verabreicht?*	☐	☐

		ja	nein
e.	**Nur für Frauen:** Nehmen Sie die „Pille“?	☐	☐
I.	☞ ***Wenn ‚ja‘:*** *Welche?* _____		
II.	Verwenden Sie andere hormonelle Verhütungsmittel?	☐	☐
III.	☞ ***Wenn ‚ja‘:*** *Welche?* _____		
IV.	Verwenden Sie andere hormonelle Präparate (z.B.: *Hormon-Ersatztherapie bei Wechseljahrbeschwerden)?*	☐	☐
V.	☞ ***Wenn ‚ja‘:*** *Welche?* _____		

4 Diabetes mellitus

a.	**Seit wann** ist bei Ihnen Diabetes bekannt? Bitte geben Sie das **Jahr** so genau wie möglich an. ☐☐☐☐ *(z.B.: 1990)*

		ja	nein
b.	Nehmen Sie Medikamente gegen Diabetes ein?	☐	☐
	☞ ***Wenn ‚nein‘, gehen Sie bitte weiter zu Frage 5.*** ☞ ***Wenn ‚ja‘:*** *Tragen Sie bitte* ***alle*** *Ihre* ***Diabetes-Medikamente*** *in die nachfolgende Tabelle ein.*		

Medikament *(z.B.: Glucophage)*	**Dosierung** *(z.B.: 3 x 500 mg)*	**Seit wann?** *(z.B.: seit 2 Jahren)*
1.		
2.		
3.		
4.		
5.		

		nie	1 Mal pro Monat oder weniger oft	2-3 Mal pro Monat	1-2 Mal pro Woche	3-6 Mal pro Woche	täglich
c.	Wie oft **vergessen** Sie Ihre Diabetes-Medikamente einzunehmen **oder** nehmen Sie **absichtlich** nicht ein?	☐	☐	☐	☐	☐	☐

5 Fragen zu Ihrem Tabak-und Alkoholkonsum

		ja	nein	nicht mehr
a.	**Rauchen** Sie?	☐	☐	☐
I.	☞ ***Wenn ‚ja':*** *Seit wie vielen Jahren rauchen Sie?*_____			
II.	☞ ***Wenn ‚ja':*** *Wie viele Zigaretten rauchen Sie ungefähr pro Tag?*_____			
III.	☞ ***Wenn ‚nicht mehr':*** *Seit wann rauchen Sie nicht mehr?*_____			
b.	Wie oft trinken Sie **Alkohol**? *(Anzahl Tage pro Woche bitte ankreuzen)*			
	[0] [1] [2] [3] [4] [5] [6] [7] **nie** **täglich**			
I.	☞ ***Falls Sie Alkohol trinken:*** *Wie viele Gläser (egal ob Bier, Wein oder Schnaps) trinken Sie durchschnittlich an einem Tag?*_____			

6 Angaben zu Ihrer Ernährung

		ja	nein
a.	Sind Sie **VegetarierIn**?	☐	☐
b.	Sind Sie **VeganerIn** (Verzicht auf tierische Produkte)?	☐	☐
c.	Wie oft nehmen Sie **Milchprodukte** zu sich? *(Anzahl Tage pro Woche bitte ankreuzen)* [0] [1] [2] [3] [4] [5] [6] [7] **nie** **täglich**		
d.	Wie oft essen Sie **Eier oder Eiprodukte**? *(Anzahl Tage pro Woche bitte ankreuzen)* [0] [1] [2] [3] [4] [5] [6] [7] **nie** **täglich**		
e.	Wie oft essen Sie **Fleisch**? *(Anzahl Tage pro Woche bitte ankreuzen)* [0] [1] [2] [3] [4] [5] [6] [7] **nie** **täglich**		

Herzlichen Dank für Ihre Bemühungen.

KANTON AARGAU

Departement
Gesundheit und Soziales
Kantonale Ethikkommission

Kantonale Ethikkommission
PD Dr. med. O. Hilfiker, Präsident
Bachstrasse 15, 5001 Aarau
Tel. Sek. + 41 (0) 62 835 29 10
Fax Sek. + 41 (0) 62 835 29 09
E-Mail marianne.wyss@ag.ch

Herr
Dr. med. Cyrill Jeger
Facharzt für Allgemeinmedizin und
Psychosomatik
Ziegelfeldstrasse 5
4600 Olten

Aarau, 21. Februar 2012/mw

Definitive Bewilligung der Studie

Studie 2012/004
Akzeptanz und biochemisches Therapieansprechen von oraler vs. intramuskulärer Vitamin B12 Supplementierung bei ambulanten Patienten

Auflagen
gemäss Beschlussmitteilung vom 2. Februar 2012

Sehr geehrter Herr Dr. Jeger

Die Kantonale Ethikkommission hat die unten aufgeführten Unterlagen mit E-Mail-Eingang vom 16. Februar 2012 zur Kenntnis genommen.

- Patientinnen- und Patienteninformation, Version vom 15. Februar 2012 mit markierten Änderungen
- Begleitschreiben vom 16. Februar 2012
- Studienprotokoll vom 15. Februar 2012
- Case Report Form vom 16. Februar 2012
- Klinische Angaben und Diagnosen vom 15. Februar 2012
- Versicherungsnachweis vom 13. Februar 2012

Den Auflagen der Kantonalen Ethikkommission gemäss der Beschlussmitteilung vom 2. Februar 2012 wurde entsprochen.

Die definitive Bewilligung der vorerwähnten Studie erfolgte am 21. Februar 2012

Freundliche Grüsse

PD Dr. med. Otto Hilfiker
Präsident der KEK AG/SO

- Kopie geht an: Herr Philipp Walter, Studienzentrum Aarelab, Industriestrasse 78 - 4600 Olten

K:\DGS-GES-Daten\INFO\DATEN\GD_KEK\Ethikkommission 2012\Briefe Investigator (Auflagen)\Februar\2012-004, Philipp Walter.doc

swissmedic

Formular für die Notifikation/Bewilligung klinischer Versuche mit Arzneimitteln und Transplantatprodukten

Bestätigung der Notifikation/Bewilligung

für klinische Versuche mit Arzneimitteln und Transplantatprodukten

Bitte ausfüllen!

Klinischer Versuch	Titel	Akzeptanz und biochemisches Therapieansprechen der oralen Vitamin B12 Substitution
	Protokoll-Nr.	Study proposal Version 2012-02-15
Sponsor	Name	Pharmaceutical Care Research Group, Departement Pharmazeutische Wissenschaften, Universität Basel
	Adresse	Pharmazentrum, Klingelbergstr. 50, 4056 Basel
CRO	Name	
	Adresse	
Vertreter in der Schweiz (gemäss VKlin Art. 7, *falls der Sponsor im Ausland ist*)	Name	
	Adresse	
IMP(s)		B12 "Ankermann" Dragées 1 mg Vitarubin® Depot Ampullen 1.0 mg / 1 ml
Hauptprüfer des Zentrums für die Erstnotifikation	Name	Dr. med. Cyrill Jeger // Dipl. pharm. Ph. Walter
	Adresse	Ziegelfeldstr. 5, 4600 Olten // Aarelab AG, Industriestr. 78, 4600 Olten

Bitte leer lassen!

Referenznummer des klinischen Versuchs 2012 DR 4 0 4 5

Hiermit wird bestätigt, dass der beschriebene klinische Versuch beim Schweizerischen Heilmittelinstitut erfasst wurde. Der klinische Versuch kann nach Erhalt dieser Bestätigung beginnen (Art. 15 Abs. 2 VKlin).

swissmedic
Schweizerisches Heilmittelinstitut
Institut suisse des produits thérapeutiques
Istituto svizzero per gli agenti terapeutici
Swiss Agency for Therapeutic Products

Bern, 29. März 2012

(Medical Reviewer Swissmedic)
Dr. med. C. Senessie

CRF VB12.004.02 Vitamin B_{12} Substitution	Prüfer Initialen	Datum (TT/MM/JJ)	Patient Code
	☐☐	☐☐☐☐☐☐	☐☐

Case Report Form (CRF)

Studie	**Orale vs. intramuskuläre Vitamin B_{12} Substitution**
Studienregister	**ClinicalTrials.gov Nr.** NCT01832129
Studienzentrum	**001 – Aarelab, Industriestr. 78, CH-4600 Olten**
Principal Investigator	**Dr. med. C. Jeger (Prüfarzt gemäss Ethik-Antrag)** **Dipl. pharm. Ph. Walter (Studienzentrum Aarelab)**

Auszufüllen durch Mitarbeitende des Studienteams.

1 Patienten Basisinformation

Ziffer			JA	NEIN
1.1	Patienten-Code	☐☐ - ☐☐☐☐		
1.2	Geschlecht	☐männlich ☐weiblich		
1.3	Geburtsdatum	☐☐ / ☐☐ / ☐☐☐☐ (TT/MM/JJJJ)		
1.4	Einverständnis-erklärung	Liegt die Einverständniserklärung für die Studienteilnahme vor? (☞falls NEIN: keine Studienteilnahme)	☐	☐
1.5	Teilnahme-beschränkung	Ist das Einverständnis auf die Akzeptanz Studie beschränkt? (☞falls JA: Einschränkung der Teilnahme auf Fragebogen Q-DN und Q-A)		
1.6	Rekrutierender Arzt	NAME Arzt ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐		
1.7	Spezialisierung	☐Allgemeinarzt ☐Gastroenterologe ☐Neurologe ☐Andere:		

2 Einschluss- und Ausschlusskriterien

Ziffer			JA	NEIN
Einschlusskriterien		(Einschluss, falls alle Fragen mit JA beantwortet)		
2.1	Alter	Patient-/in ist mindestens 18 Jahre alt	☐	☐
2.2	VB12-Test	Es liegt eine ärztliche Verordnung zur Bestimmung des Vitamin B12 Status des Patienten / der Patientin vor	☐	☐
2.3.	Einverständnis-erklärung	Der Patient hat den Ablauf der Studie verstanden, wurde über die Folgen einer Studienteilnahme informiert und hat freiwillig sein Einverständnis zur Studienteilnahme gegeben.	☐	☐
Ausschlusskriterien		(Ausschluss, falls mind. 1 Frage mit JA beantwortet)		
2.4.	Konsum von VB12 Präparaten	Der Patient hat innerhalb des dem Studienteilnahme vorangehenden Monates pharmazeutische Präparate konsumiert, welche Einfluss auf die Vitamin B_{12} Versorgungslage haben können.	☐	☐
2.5.	Diagnostizierte Demenz	Bei dem / der Patient-/in wurde in der Vergangenheit eine Demenz diagnostiziert.	☐	☐
2.6.	Transcobolamin Transporter Defekt	Bei dem / der Patient/-in liegt ein bekannter vererbbarer Defekt des Transcobolamin Transporters vor	☐	☐
2.6.	Sprachliche Verständigung	Mit dem Patienten / der Patientin ist keine ausreichende Verständigungsmöglichkeit auf Deutsch, Französisch, Italienisch oder Englisch möglich	☐	☐

CRF VB12.004.02 Vitamin B_{12} Substitution	Prüfer Initialen	Datum (TT/MM/JJ)	Patient Code
	☐☐	☐☐☐☐☐☐	☐☐

3 Fragebogen Q-DN (Demographie und Ernährung) und Q-A (Akzeptanz)

- Quelldokument **Q-DN** und (durch Patient ausgefüllte Fragebogen) beiliegen
- Quelldokument **Q-A** (bei Telefoninterview durch Studienmitarbeiter auszufüllen) beilegen

4 Baseline Visit (V0, Arztpraxis)

*Die Daten werden in der Arztpraxis durch Praxismitarbeiter, welche durch den Studienleiter entsprechend geschult wurden erfasst. Die Daten werden auf einem nicht anonymisierten Quelldokument (**F-V0**) erfasst und an das Studienzentrum übermittelt. Die Übertragung der Daten in das CRF erfolgt durch Mitarbeitende des Studienzentrums.*

Ziffer		JA	NEIN
4.1	Datum des Baseline Visits ☐☐/☐☐/☐☐ (TT/MM/JJ) ☐☐:☐☐ (HH:MM)		
4.2	Vitamin B12 Resultat liegt vor	☐	☐
4.3	Die Voraussetzungen für eine Studienteilnahme gemäss Ziff. 1 und 2 sind gegeben	☐	☐
4.4	Es besteht eine Indikation zur Substitution mit Vitamin B12 (☞ *f*alls NEIN: Beschränkung auf Akzeptanz Studie → STOPP) (☞ *f*alls JA: weiter mit Ziff 4.5)	☐	☐
4.5	Die folgende Behandlungsart wurde dem Patienten durch die Randomisierung zugewiesen: ☐oral ☐intramuskulär		
4.6	Die Baseline Blutprobe konnte entnommen werden:	☐	☐
	Datum: ☐☐/☐☐/☐☐ (TT/MM/JJ) *Zeit:* ☐☐:☐☐ (HH:MM)		
4.7	VB12 i.m.: die erste Dosis Vitarubin Depot konnte injiziert werden	☐	☐
	*<u>Hinweis</u>: Die intramuskulären Injektionen in der entsprechenden Behandlungsgruppe sind im **Medikamenten-Administrationsprotokoll (Quelldokument F-MED)** zu dokumentieren!*		
	VB12 oral: die Verwendung des Medikamentenblisters konnte erläutert werden und die erste Dosis konnte durch den Patienten entnommen werden	☐	☐
	Datum: ☐☐/☐☐/☐☐ (TT/MM/JJ) *Zeit:* ☐☐:☐☐ (HH:MM)		
4.8	Die gemäss Studienprotokoll erforderlichen Termine in der Arztpraxis (i.m. Injektionen) und im Studienzentrum (Kontrolluntersuchungen) konnten mit dem Patienten vereinbart werden.	☐	☐
4.9	Quelldokument Terminvereinbarungen (F-TER) liegt vor?	☐	☐
	Studienmedikation wurde ausgehändigt (orale Behandlung)?	☐	☐
4.10	Diagnoseliste (Q-GP) wurde mitgeliefert (☞ *f*alls NEIN: aus Arztpraxis anfordern)	☐	☐
4.11	Bestätigung des ausführenden Mitarbeiters, dass die Schritte in Ziff. 4.1 bis 4.10. wie vorgesehen durchgeführt liegt vor?	☐	☐

CRF VB12.004.02 Vitamin B_{12} Substitution	Prüfer Initialen	Datum (TT/MM/JJ)	Patient Code
	☐☐	☐☐/☐☐/☐☐	☐☐

5 Erster Visit (V7, Studienzentrum)

Ziffer		JA	NEIN
5.1	Datum des Besuchs ☐☐/☐☐/☐☐ (TT/MM/JJ) ☐☐:☐☐ (HH:MM)		
5.2	Venöse Blutentnahme: Zeitpunkt auf Laborauftragsformular (**F-LAB**) dokumentiert?	☐	☐
5.3	VB12 oral: Compliance-Daten ausgelesen?	☐	☐
	VB12 oral: Anzahl der entnommenen Einheiten entspricht der Anzahl bisher einzunehmenden Einheiten? (falls NEIN: Anzahl abweichende Einheiten: V0 bis V7 ☐☐)	☐	☐
	VB12 i.m.: Einhaltung des Therapie-Protokolls konnte verifiziert werden?	☐	☐
5.4	Liste aller verordneter Medikamente (**F-MV**) wurde ausgefüllt?	☐	☐

6 Zweiter Visit (V14, Studienzentrum)

Ziffer		JA	NEIN
6.1	Datum des Besuchs ☐☐/☐☐/☐☐ (TT/MM/JJ) ☐☐:☐☐ (HH:MM)		
6.2	Venöse Blutentnahme: Zeitpunkt auf Laborauftragsformular (**F-LAB**) dokumentiert?	☐	☐
6.3	VB12 oral: Compliance-Daten ausgelesen?	☐	☐
	VB12 oral: Anzahl der entnommenen Einheiten entspricht der Anzahl bisher einzunehmenden Einheiten? (falls NEIN: Anzahl abweichende Einheiten V7-V14: ☐☐)	☐	☐
	VB12 i.m.: Einhaltung des Therapie-Protokolls konnte verifiziert werden?	☐	☐

7 Dritter Visit (V28, Studienzentrum)

Ziffer		JA	NEIN
7.1	Datum des Besuchs ☐☐/☐☐/☐☐ (TT/MM/JJ) ☐☐:☐☐ (HH:MM)		
7.2	Venöse Blutentnahme: Zeitpunkt auf Laborauftragsformular (**F-LAB**) dokumentiert?	☐	☐
7.3	VB12 oral: Compliance-Daten ausgelesen <u>und</u> Medikamentenblister zurückgegeben?	☐	☐
	VB12 oral: Anzahl der entnommenen Einheiten entspricht der Anzahl bisher einzunehmenden Einheiten? (falls NEIN: Anzahl abweichende Einheiten V14-V28: ☐☐)	☐	☐
	VB12 i.m.: Einhaltung des Therapie-Protokolls konnte verifiziert werden?	☐	☐
7.4	<u>Instruktion zum Abschluss:</u> • Den Patienten informieren, dass über die Studienteilnahme ein Bericht zu Handen des Arztes erstellt wird und die Resultate für die Weiterführung der Behandlung (falls erforderlich) zur Verfügung stehen. • Verifizieren, dass dem Patienten sein nächster Termin für eine ärztliche Konsultation bekannt ist. • Dem Patienten zum Abschluss der Studienteilnahme Gelegenheit bieten, Fragen zu stellen.		

CRF VB12.004.02 Vitamin B_{12} Substitution	Prüfer Initialen	Datum (TT/MM/JJ)	Patient Code
	☐☐	☐☐☐☐☐☐	☐☐

8 Medikamenten-Verabreichungsprotokoll (Vitamin B12 Substitution)

Ziffer		JA	NEIN
7.1	i.m. Behandlung: Alle Injektionen konnten termingerecht ausgeführt werden (falls NEIN: Abweichung auf Verabreichungsprotokoll (F-MED) dokumentiert, übertragen auf Ziff. 7.2)	☐	☐
	Orale Substitution: alle während der Studiendauer einzunehmenden oralen Dosen wurden eingenommen (falls NEIN: Abweichung in Ziff. 7.2. eingetragen)	☐	☐
7.2	Art und Umfang der Abweichung vom vorgesehenen Verabreichungsschema ☐ nicht alle Dosen eingenommen / injiziert (Anzahl fehlende Dosen: ☐☐) ☐ alle Dosen eingenommen / injiziert, aber nicht zur vorgesehenen Zeit		

9 Laborresultate

Die Laborresultate der Visits V0, V7, V14 und V28 sind als Befundausdrucke dem CRF beizulegen.

Ziffer		JA	NEIN
8.1	Sind die Laborresultate aller Visits vollständig vorhanden?	☐	☐
8.2	Sind die korrespondierenden Proben der Visits V0, V7, V14 und V28 in der Studienserothek vorhanden.	☐	☐

10 Klinische Angaben und Diagnosen

Ziffer		JA	NEIN
10.1	Diagnoseliste (Q-GP) liegt vor?	☐	☐

CRF VB12.004.02 Vitamin B_{12} Substitution	Prüfer Initialen	Datum (TT/MM/JJ)	Patient Code

Checklist Quelldokumente

Bitte prüfen Sie bei Abschluss der Studienteilnahme, ob alle unten aufgeführten Quelldokumente vorhanden und vollständig ausgefüllt sind. Bei Patienten mit eingeschränkter Teilnahme aufgrund von Ziff. 1.5 oder 4.4. sind nur die Dokumente Nr. 1-3 und 6 erforderlich.

A = Anonymisiert
P = Personalisiert
SZ = Auszufüllen durch Studienmitarbeiter

	Code	Typ	Bezeichnung	A/P	Auszufüllen durch:	Vollständig? Visum
1	F-IC	Formular	Unterzeichnete Einverständniserklärung	P	Patient +SZ	
2	Q-DN	Fragebogen	Demographie und Ernährung	A	Patient	
3	Q-A	Fragebogen	Interviewprotokoll	A	SZ	
4	F-V0	Formular	Dokumentation V0 (Arztpraxis)	P	Praxis	
5	F-TER	Formular	Terminblatt Visits in Arztpraxis und Studienzentrum	P	Praxis	
6	Q-GP	Fragebogen	Klinische Angaben und Diagnosen	A	Praxis	
7	F-MED	Formular	Medikamenten-Administrationsprotokoll	P	Patient	
8	F-MV	Formular	Liste der verordneten Medikamente	A	Patient	
9	F-LAB	Formular	Laborresultate V0, V7, V14, V28	A	SZ	

IHAMB

DEPARTMENT OF PHARMACEUTICAL SCIENCES

solothurner spitäler ag

Studienkoordination
Tel. 079 548 47 28
062 212 58 00
corina.metaxas@unibas.ch

Einverständniserklärung zur Studienteilnahme

Titel der Studie:	**Substitutionsbehandlung mit Vitamin B_{12}**
Ort der Studie:	Olten (SO)
Prüfärztin/Prüfarzt Name und Adresse:	Gruppenpraxis Bifang, Aarauerstrasse 55, 4600 Olten
Patientin/Patient NAME und Vorname: Geburtsdatum: Geschlecht:	.... / ..... / ..... (TT / MM / JJJJ) ☐ männlich ☐ weiblich
Teilnahmebeschränkung:	☐ Ich möchte nur an der Erhebung mittels Fragebogen teilnehmen.

- Ich wurde vom unterzeichnenden Studienmitarbeiter mündlich und schriftlich über die Ziele, den Ablauf der Studie und über mögliche Vor- und Nachteile sowie allfällige Risiken informiert.
- Ich habe die zur oben genannten Studie abgegebene schriftliche Patienteninformation vom 16.05.13 gelesen und verstanden. Meine Fragen im Zusammenhang mit der Teilnahme an dieser Studie sind mir zufriedenstellend beantwortet worden. Ich kann die schriftliche Patienteninformation behalten und erhalte eine Kopie meiner schriftlichen Einverständniserklärung.
- Ich hatte genügend Zeit, um meine Entscheidung zu treffen.
- Ich bin darüber informiert, dass eine Versicherung Schäden deckt, falls solche im Rahmen der Studie auftreten.
- Ich weiss, dass meine persönlichen Daten nur in anonymisierter Form an aussenstehende Institutionen zu Forschungszwecken weitergegeben werden. Ich bin einverstanden, dass die zuständigen Fachleute des Studienauftraggebers, der Behörden und der Kantonalen Ethikkommission zu Prüf- und Kontrollzwecken in meine Originaldaten Einsicht nehmen dürfen, jedoch unter strikter Einhaltung der Vertraulichkeit.
- Ich nehme an dieser Studie freiwillig teil. Ich kann jederzeit und ohne Angabe von Gründen meine Zustimmung zur Teilnahme widerrufen, ohne dass mir deswegen Nachteile bei der weiteren medizinischen Betreuung entstehen.
- Ich bin damit einverstanden, dass die Resultate meinem behandelnden Arzt zur Verfügung gestellt werden.

Ort, Datum	Unterschrift der Patientin/des Patienten

Bestätigung des Studienmitarbeiters (mit der Besprechung der Einwilligungserklärung betraut): Hiermit bestätige ich, dass ich diesem Patienten/dieser Patientin Wesen, Bedeutung und Tragweite der Studie erläutert habe. Ich versichere, alle im Zusammenhang mit dieser Studie stehenden Verpflichtungen zu erfüllen. Sollte ich zu irgendeinem Zeitpunkt während der Durchführung der Studie von Aspekten erfahren, welche die Bereitschaft des Patienten/der Patientin zur Teilnahme an der Studie beeinflussen könnten, werde ich ihn/sie umgehend darüber informieren.

Ort, Datum	Unterschrift des Studienmitarbeiters

☞ Bitte beachten Sie auch die Frage auf der Rückseite.

IHAMB

DEPARTMENT OF PHARMACEUTICAL SCIENCES

soH solothurner spitäler ag

Studienkoordination
Tel. 079 548 47 28
062 212 58 00
corina.metaxas@unibas.ch

Unabhängige Befragung

Im Zusammenhang mit der wissenschaftlichen Fragestellung, welche durch die vorliegende Studie zur Vitamin B_{12} Substitutionsbehandlung beforscht wird, können gegebenenfalls weiter Fragen entstehen, welche gegebenenfalls durch eine weitere Studie beforscht werden soll. Deshalb kann es sein, dass wir Sie zu diesem Zeitpunkt gerne erneut anfragen. Damit wir Sie zu diesem Zweck kontaktieren dürfen, ist allerdings Ihre Zustimmung erforderlich.

Wir bitten Sie deshalb, die folgende Frage durch ankreuzen (☒) mit JA oder NEIN zu beantworten:

Ich bin einverstanden, dass ich zu einem späteren Zeitpunkt von Ihrer Forschungsgruppe wieder kontaktiert werde und angefragt werde, ob ich an einer Folgestudie teilnehmen möchte.	☐ JA	☐ NEIN

Ort, Datum	Unterschrift der Patientin/des Patienten

IHAMB

DEPARTMENT OF PHARMACEUTICAL SCIENCES

soH solothurner spitäler ag

Studienkoordination
Tel. 079 548 47 28
062 212 58 00
corina.metaxas@unibas.ch

Q-ND

Fragebogen zur Person und der Ernährung

Bitte füllen Sie folgenden Fragebogen aus.

Geburtsdatum: ...../...../..... *(Tag/Monat/Jahr)*	Geschlecht : ..... *(weiblich/männlich)*

1. Persönliche Angaben

1.1	Körpergrösse *[m]:* .....
1.2	Körpergewicht *[kg]* .....
1.3	Haben Sie in den letzten drei Monaten Gewicht verloren? ☐ Ja ☐ Nein ☐ Nicht bekannt
	➢ Wenn ‚Ja': Wie viel? ☐ weniger als 1 Kg ☐*zwischen 1 und 3kg* ☐*> 3 kg*
1.4	Haben Sie in den letzten drei Monaten an psychischem Stress oder an einer akuten Krankheit gelitten? ☐ Ja ☐ Nein
1.5	Leiden Sie an depressiven Verstimmungen oder an Depressionen? ☐ Ja ☐ Nein
1.6	Nehmen Sie Medikamente ein, welche die Stimmung aufhellen? (Antidepressiva) ☐ Ja ☐ Nein
	Wenn ‚Ja': Welche? ....
1.7	Hat schon einmal eine Vitamin B_{12} Therapie stattgefunden? ☐ Ja ☐ Nein
1.8	Haben Sie schon einmal eine Therapie mit Spritzen erhalten? ☐ Ja ☐ Nein

2. Risikofaktoren

Nikotinkonsum	
2.1	Rauchen Sie? ☐ Ja ☐ Nein ☐*Nicht mehr*
	Wenn ‚Ja': Wie lange rauchen Sie bereits? ……
	Wenn ‚Ja': Wie viele Zigaretten rauchen Sie pro Tag? ……
	Wenn ‚Nicht mehr': Seit wann rauchen Sie nicht mehr? ……

Medikamenteneinnahme	
2.2	Nehmen Sie Medikamente gegen Magensäure bedingte Erkrankungen ein? Beispielsweise gegen Sodbrennen oder Magenschmerzen. ☐ Ja ☐ Nein
	Wenn ‚Ja': Welche? ……
2.3	Nehmen Sie Medikamente gegen Blutzucker (Diabetes) ein? ☐ Ja ☐ Nein
	Wenn ‚Ja': Welche? ……
2.4	Nehmen Sie Medikamente ein, welche die Gedächtnisleistung unterstützen? ☐ Ja ☐ Nein
	Wenn ‚Ja': Welche? ……
2.5	Nur für Frauen: Nehmen Sie die Antibabypille? ☐ Ja ☐ Nein
	Wenn ‚Ja': Welche? ……

Alkoholkonsum	
2.6	Wie oft trinken Sie Alkohol? *[nie, 1-2x pro Woche, 3-4x pro Woche, 5-6x pro Woche, >6x pro Woche]* ☐*nie* ☐*1-2x pro Woche* ☐*3-4x pro Woche* ☐*5-6x pro Woche* ☐*>6x pro Woche*
	Wie viele Gläser (egal ob Bier, Wein oder Schnaps) trinken Sie an so einem Tag? ……

3. Ernährung

3.1	Wie oft essen Sie Fleisch*?* ☐*nie* ☐*1-3x pro Woche* ☐*4-6x pro Woche* ☐*täglich*
	Wenn ‚nie': Wie lange verzichten Sie bereits auf Fleisch? ……
3.2	Wie oft essen oder trinken Sie Milchprodukte*?* ☐*nie* ☐*1-3x pro Woche* ☐*4-6x pro Woche* ☐*täglich*
3.3	Wie oft essen Sie Eier oder Eiprodukte? ☐*nie* ☐*1-3x pro Woche* ☐*4-6x pro Woche* ☐*täglich*
3.4	Haben Sie in den letzten drei Monaten aufgrund von Appetitlosigkeit, Verdauungs- oder Schluckproblemen weniger Nahrung als üblich zu sich genommen? ☐ Ja ☐ Nein ☐ ein wenig

Vielen Dank für das Ausfüllen des Fragebogens!

IHAMB

DEPARTMENT OF PHARMACEUTICAL SCIENCES

solothurner spitäler a

Q-A

Tel. 079 548 47 28
062 212 58 00
corina.metaxas@unibas.ch
www.pharmacare.unibas.ch

Fragebogen zur Vitamin B12 Studie

Ihr Arzt hat Ihnen Blut abgenommen um abzuklären, ob Sie an einem Vitamin B_{12} Mangel leiden.

Stellen Sie sich nun vor, dass sich der Verdacht bestätigt und Sie tatsächlich mehr Vitamin B_{12} brauchen. Der Arzt erklärt Ihnen, dass es zwei Therapiemöglichkeiten gibt. Zur Auswahl stehen a) Vitamin Spritzen oder b) Vitamin Tabletten. Beide Behandlungen wirken gleich gut und haben ähnliche Nebenwirkungen.

1	**Welche der beiden Behandlungsoptionen bevorzugen Sie?** ☐ Tabletten ☐ Spritzen ☐ egal
2	**Wie oft gehen Sie zum Arzt?** ☐ ca. 1 mal pro Woche ☐ ca. 1 mal pro Monat ☐ ca. 1 in pro halbes Jahr ☐ ca. 1 mal im Jahr

Bitte beantworten Sie die folgenden Fragen auf einer Skala von 1-10 mit einem Kreuz im dazugehörigen Feld.

3	**Wie sicher fühlen Sie sich in Bezug auf die Wirkung der Therapie, wenn diese beim Arzt durchgeführt wird?** ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 1= sehr unsicher 10= sehr sicher
4  	**Wie schmerzhaft, schätzen Sie ist es** **a) eine Spritze zu erhalten?** ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 1 =gar nicht schmerzhaft 10= schlimmster Schmerz **b) eine Tablette zu schlucken?** ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 1 =gar nicht schmerzhaft 10= schlimmster Schmerz

Version 16.05.13

IHAM*B*

DEPARTMENT OF PHARMACEUTICAL SCIENCES

solothurner spitäler a

Q-A

Tel. 079 548 47 28
062 212 58 00
corina.metaxas@unibas.ch
www.pharmacare.unibas.ch

5  	**Wie eklig finden Sie es** **a) eine Spritze zu erhalten?** ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 1=sehr appetitlich 10= sehr eklig **b) eine Tablette zu einzunehmen?** ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 1=sehr appetitlich 10= sehr eklig
6  	**Wie sehr fürchten Sie sich vor den Nebenwirkungen** **a) der Therapie mit der Spritze?** ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 1=ich fürchte mich überhaupt nicht 10= ich fürchte mich sehr **b) der Therapie mit den Tabletten?** ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 1=ich fürchte mich überhaupt nicht 10= ich fürchte mich sehr
7  	**Wie <u>wirksam</u> denken Sie ist die Therapie** **a) mit den Spritzen?** ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 1= unwirksam 10= sehr wirksam **b) mit den Tabletten?** ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 1= unwirksam 10= sehr wirksam
8  	**Wie <u>angenehm</u> finden Sie es** **a) eine Spritze von ihrem Arzt zu erhalten?** ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 1= sehr angenehm 10= sehr unangenehm **b) eine Tablette einzunehmen?** ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 1= sehr angenehm 10= sehr unangenehm

Version 16.05.13

IHAMB

DEPARTMENT OF PHARMACEUTICAL SCIENCES

solothurner spitäler a

Tel. 079 548 47 28
062 212 58 00
corina.metaxas@unibas.ch
www.pharmacare.unibas.ch

Q-A

9  	**Wie viel Schwierigkeiten bereitet es Ihnen** **a) eine Spritze von ihrem Arzt zu erhalten?** ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 1= keine Schwierigkeiten 10= sehr grosse Schwierigkeiten **b) eine Tablette aus der Verpackung zu entnehmen und einzunehmen?** ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 1= keine Schwierigkeiten 10= sehr grosse Schwierigkeiten

Für die Therapie, die als Spritze verabreicht wird, ist zumindest zu Beginn der Therapie 1 Arztbesuch pro Woche erforderlich. Die Tabletten müssen jeden Tag zu Hause eingenommen werden.

10  	**Wie gross schätzen Sie Ihren zeitlichen Aufwand für das** **a) Erhalten der Spritze ein?** ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 1=sehr geringer Aufwand 10= sehr grosser Aufwand **b) Einnehmen der Tabletten ein?** ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 1=sehr geringer Aufwand 10= sehr grosser Aufwand
11  	**Wie gross schätzen Sie Ihren finanziellen Aufwand für das** **a) Erhalten der Spritze ein?** ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 1=keine finanzielle Belastung 10= sehr grosse finanzielle Belastung **b) Einnehmen der Tabletten ein?** ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 1=keine finanzielle Belastung 10= sehr grosse finanzielle Belastung

Version 16.05.13

IHAMB

DEPARTMENT OF PHARMACEUTICAL SCIENCES

solothurner spitäler a

Tel. 079 548 47 28
062 212 58 00
corina.metaxas@unibas.ch
www.pharmacare.unibas.ch

Q-A

12  	**Wie viel Mühe bereitet es Ihnen,** **a) sich einmal in der Woche an den Termin beim Arzt zur Erhaltung der Spritze zu erinnern?** ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 1= keine Mühe 10= sehr viel Mühe **b) sich jeden Tag an die Einnahme von Tabletten zu erinnern?** ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 1= keine Mühe 10= sehr viel Mühe

Je nach Ausmass und Ursache des Vitamin B12 Mangels kann die Therapie länger dauern oder muss sogar lebenslänglich fortgesetzt werden.

13	**Würden sie Ihre Wahl ändern, wenn eine längere oder lebenslange Therapienotwendig wäre?** ☐ Ja ☐ Nein
14	**Wenn ja, welche Therapieform würden Sie wählen?** ☐ Tabletten ☐ Spritzen ☐ egal

Vielen Dank für das Ausfüllen des Fragebogens! Sämtliche Angaben werden vertraulich behandelt und nur in anonymisierter Form ausgewertet. Je nach dem wird sie das Studienzentrum für eine weitere Befragung in einem Monat kontaktieren. Dafür benötigen wir ihre Angaben:

Name, Vorname: .....

Adresse: .....

.....

Telefonnummer: .....

Version 16.05.13

QD-B1 Vitamin B12 Studie		Prüfer Initialen	Patient ID
		☐☐	☐☐

Terminvereinbarung für Studienteilnahme

☞ *Bitte vereinbaren Sie mit dem Patienten die erforderlichen Termine in der Arztpraxis und im* Kantonsspital Olten . *Notieren Die diese auf dem vorliegenden Blatt und geben Sie dem Patienten eine Kopie mit und senden Sie eine weitere Kopie per Kurier ans Studienzentrum.*

Patientenidentifikation

Name und Vorname: ……
Geburtsdatum ……/……/……(TT/MM/JJJJ)
Weiblich (w)/ Männlich (m) ……

Behandlungsgruppe: intramuskuläre Injektionen (Spritzen)

Hinweise für die Terminplanung:

Intramuskuläre Injektionen

Die Injektionen sind nach Möglichkeit in wöchentlichen Abständen einzuplanen. Abweichungen +/- 1 Tag sind zulässig. Die Blutentnahme sollte am gleichen Termin stattfinden, ist aber vor der Injektion durchzuführen. Falls die Blutentnahme ausnahmsweise im Studienzentrum stattfinden sollte, sind die Termine vor der Injektion einzuplanen.

Termine im Studienzentrum

Termine für die Besuche im Kantonsspital Olten können Mo-Fr von 8.00 – 17.00 h durchgehend eingeplant werden. Termine ausserhalb der Öffnungszeiten sind möglich, müssen aber vorher mündlich abgesprochen werden. Bei Zugehörigkeiten zur Behandlungsgruppe mit intramuskulären Injektionen soll der Termin im Studienzentrum jeweils vor dem Termin in der Arztpraxis stattfinden.

Visit	Datum (TT/MM/JJ)	Zeit (HH:MM)	Wo?	Was?
V7			Arztpraxis	Blutentnahme und Vitamin B12 Injektion
V14			Arztpraxis	Blutentnahme und Vitamin B12 Injektion
V21			Arztpraxis	Vitamin B12 Injektion
V28			**Achtung:** dieser Termin findet im Kantonsspital Olten statt	Letzte Blutentnahme

Bemerkungen
……
……
……

Rückfragen
Bei Fragen können Sie sich gerne direkt an das Studienzentrum wenden.

Studienkoordination
Corina Metaxas
Pharmaceutical Care Research Group
Universität Basel
T 079 548 47 28

QD-B1 Vitamin B12 Studie		Prüfer Initialen	Patient ID
		☐☐	☐☐

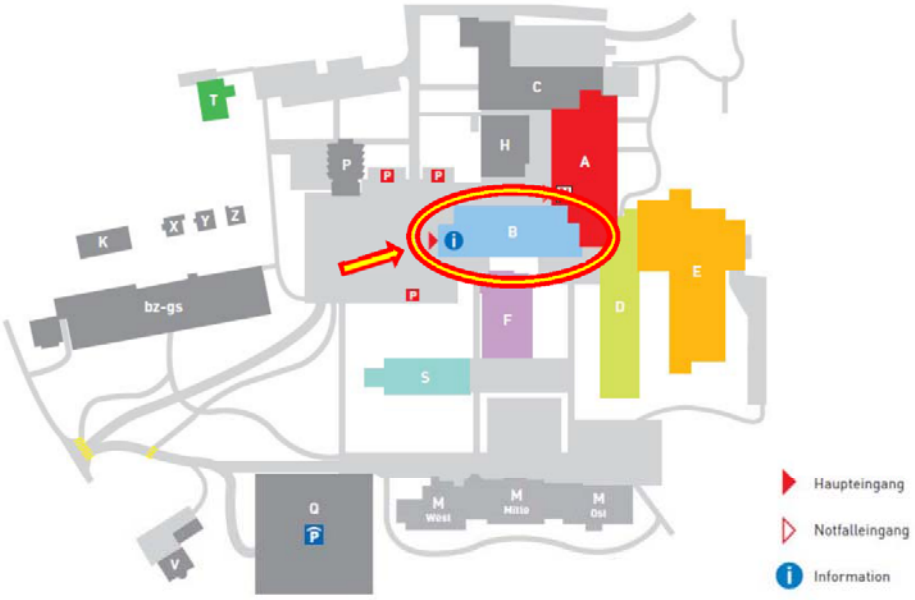
So erreichen Sie uns:

Zu Fuss vom Bahnhof Olten (10 Minuten): Ausgang Stadt benutzen, über die Bahnhofbrücke gehen und dann nach rechts in den Amthausquai (der Aare entlang) biegen, nach 400 Metern links über einen kurzen Waldweg zum Spital (Wegweiser beachten).

Mit öffentlichen Verkehrsmitteln vom Bahnhof (5 Minuten): Ausgang Stadt benutzen und mit dem Bus Linie 2 (Richtung Trimbach) bis Haltestelle Kantonsspital fahren.

Mit dem Auto: In Olten Richtung Trimbach/Basel fahren. Das Spital befindet sich 500 Meter vom Stadtzentrum entfernt auf der rechten Seite. Gebührenpflichtige Parkzonen vorhanden.

Die Blutentnahmen finden im ersten Stock des markierten Gebäudes (Haupteingang) im Kantonsspital Olten statt. Bei der Information wird man Ihnen Auskunft geben, wie Sie das Institut für Labormedizin finden.



Institut für Labormedizin
Kantonsspital Olten
Baslerstrasse 150
4600 Olten
Tel. 062 311 51 01
079 548 47 28

soH
solothurner spitäler ag

QD-B1 Vitamin B12 Studie		Prüfer Initialen	Patient ID
		☐☐	☐☐

Protokoll Baseline Visit (V0)

Einschlusskriterien

Ziffer		JA	NEIN
4.1	Datum des Besuchs ☐☐ ☐☐ ☐☐ (TT/MM/JJ) ☐☐ ☐☐ (HH:MM)		
4.2	Liegen die Serumvitamin B_{12} - Werte aus dem Laborbefund B_S unter 200 pmol / Liter?	☐	☐
4.3	Ist die Indikation für eine Vitamin B_{12} Supplementierung gegeben? *(☞ falls NEIN: Beschränkung auf Akzeptanzstudie→STOPP)*	☐	☐
4.4	Ist die sprachliche Verständigungsmöglichkeit für die Studienteilnahme ausreichend?	☐	☐
4.5	Patient/-in ist mindestens 18 Jahre alt?	☐	☐
4.6	*Der Patient hat im vorangehenden Monat keine pharmazeutischen Präparate konsumiert, welche Einfluss auf die Vitamin B12 Versorgungslage haben?*	☐	☐
4.7	*Der Patient hat keine bestehende Diagnose:* • *Diagnostizierte Demenz* • *Transcobolamin Transporter Defekt*	☐	☐
4.8	Liegt die unterzeichnete informierte Einverständniserklärung F_IC vor? *(☞ falls NEIN → Formular unterzeichnen lassen)*	☐	☐
	ⓘ Ziff. 4.2 bis 4.8 stellen Einschlusskriterien dar. Ist eine der Fragen 4.2 bis 4.8 nicht mit JA beantwortet, kann der Patient nicht in die Studie aufgenommen werden.		

Allgemeine Angaben

Ziffer		JA	NEIN
4.9	Wurde der Fragebogen Q-ND vom Patienten ausgefüllt und zurückerhalten? *falls NEIN → Fragebogen jetzt ausfüllen lassen*	☐	☐
4.10	Wurde der Fragebogen Q-A vom Patienten ausgefüllt und zurückerhalten? *falls NEIN → Fragebogen jetzt ausfüllen lassen*	☐	☐
4.11	Wurde das Formular F_MV ausgefüllt und mit dem Patienten ergänzt?	☐	☐

Instruktionen

Ziffer		JA	NEIN
4.12	*Bitte dokumentieren Sie alle Blutentnahmen und Vitarubin Depotinjektionen jeweils im separaten Studienprotokoll.*		
4.13	Die gemäss Studienprotokoll erforderlichen Termine für die nächsten Blutentnahmen und i.m. Applikationen konnten mit dem Patienten vereinbart werden?	☐	☐
4.14	Bitte stellen sie folgende Unterlagen für das Studienzentrum zusammen(Versand Pat_V0): • Unterzeichnete Einverständniserklärung (Original) • Fragebogen Q-ND • Fragebogen Q-A • Formular F-MV • Blutprobe B_0 • Kopie: beide Seiten dieses Studienprotokolls V0	☐	☐

Bestätigung des ausführenden Mitarbeiters, dass die Schritte in Ziff.4.1 bis 4.14 wie vorgesehen durchgeführt werden konnten:

Datum: ☐☐ ☐☐ ☐☐ (TT/MM/JJ) Visum:

QD-B1 Vitamin B12 Studie		Prüfer Initialen	Patient ID
		☐☐	☐☐

Studienprotokoll: Visits V_0 bis V_21

Bitte protokollieren Sie bei jedem Visit die zugehörigen Spalten in der Tabelle:

Visit		JA	NEIN
V0	Datum des Besuchs ☐☐/☐☐ ☐☐ (TT/MM/JJ)		
	Zeitpunkt der Blutentnahme ☐☐ ☐☐ (HH:MM)		
	Vitarubin Depot wurde appliziert zum Zeitpunkt ☐☐ ☐☐ (HH:MM)		
	Der Schmerzscore konnte ermittelt werden -> Gemessener Wert: ☐	☐	☐
	Fragebogen Q_A_wurde vom Patienten ausgefüllt und zurückerhalten?	☐	☐
	Versand Pat_V0 zusammengestellt und umgehend an das Studienzentrum retourniert	☐	☐
	Visum Mitarbeiter : ……		
V7	Datum des Besuchs ☐☐/☐☐ ☐☐ (TT/MM/JJ)		
	Der Visit wurde termingerecht wahrgenommen? (☞ *falls NEIN → Bitte nebenan notieren)*	☐	☐
	Zeitpunkt der Blutentnahme ☐☐ ☐☐ (HH:MM)		
	Vitarubin Depot wurde appliziert zum Zeitpunkt ☐☐ ☐☐ (HH:MM)		
	Der Schmerzscore konnte ermittelt werden -> Gemessener Wert: ☐	☐	☐
	Fragebogen Q_A_7 wurde vom Patienten ausgefüllt und zurückerhalten?	☐	☐
	Visum Mitarbeiter : ……		
V14	Datum des Besuchs ☐☐ ☐☐ ☐☐ (TT/MM/JJ)		
	Der Visit wurde termingerecht wahrgenommen? (☞ *falls NEIN → Bitte nebenan notieren)*	☐	☐
	Zeitpunkt der Blutentnahme ☐☐ ☐☐ (HH:MM)		
	Vitarubin Depot wurde appliziert zum Zeitpunkt ☐☐ ☐☐ (HH:MM)		
	Der Schmerzscore konnte ermittelt werden -> Gemessener Wert:	☐	☐
	Fragebogen Q_A_14 wurde vom Patienten ausgefüllt und zurückerhalten?	☐	☐
	Visum Mitarbeiter : ……:		
V21	Datum des Besuchs ☐☐/☐☐ ☐☐ (TT/MM/JJ)		
	Der Visit wurde termingerecht wahrgenommen? (☞ *falls NEIN → Bitte nebenan notieren)*	☐	☐
	Vitarubin Depot wurde appliziert zum Zeitunkt ☐☐ ☐☐ (HH:MM)		
	Der Schmerzcore konnte ermittelt werden -> Gemessener Wert: ☐	☐	☐
	Visum Mitarbeiter : ……		

QD-B1 Vitamin B12 Studie		Prüfer Initialen	Patient ID
		☐☐	☐☐

Bitte übermitteln Sie die ausgefüllten Fragebogen Q_A_7 und Q_A_14 und sowie dieses Studienprotokoll nach dem letzten Visit per Kurier an das Studienzentrum.

Dieses Protokoll bleibt bis zum letzten Besuchs des Patienten zum Zeitpunkt V 21 in ihrer Arztpraxis.

Bemerkungen:

……

……

……

……

……

……

……

……

……

……

……

……

……

……

……

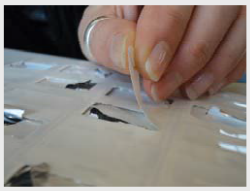
……

Entnahmeanleitung

Elektronische Tablettenblister

1. Drücken Sie die Tablette aus dem Blister.

2. Entfernen Sie die Plastiklasche auf der Rückseite **vollständig**




Medikationsset
Orale Vitamin B12 Substitution
Sehr geehrte Patientin, sehr geehrter Patient
Für Ihre Einwilligung zur Teilnahme an der Studie danken wir Ihnen vielmals. Sie wurden zufällig zu der Behandlung mit Tabletten zugeteilt.
Pro Tag sollten Sie jeweils **am abend** eine Tablette unzerkaut mit etwas Flüssigkeit einnehmen.
Sie bekommen einen Tablettenblister, der den Entnahmezeitpunkt elektronisch registriert. Bitte nehmen Sie die Tablette direkt nach der Entnahme aus dem Blister ein!
Vielen Dank für Ihre Mithilfe!
Bei Fragen, Unklarheiten oder Problemen mit dem Tablettenblister können Sie sich jederzeit bei der Studienleitung im Aarelab melden.
Studienkoordination
Pharmaceutical Care Research Group
Corina Metaxas
T 079 548 47 28
corina.metaxas@unibas.ch

QD-B1 Vitamin B12 Studie	Besuch 1	Prüfer Initialen	Patient ID
		☐☐	☐☐

Terminvereinbarung für Studienteilnahme

☞ Bitte vereinbaren Sie mit dem Patienten die erforderlichen Termine in der Arztpraxis. Notieren Die diese auf dem vorliegenden Blatt ,geben Sie dem Patienten eine Kopie mit und schicken Sie eine weitere Kopie im Versand_Pat_V0 per Fax (Aarelab, Fax 062 212 58 06) oder Kurier ans Studienzentrum.

Patientenidentifikation

Name und Vorname: ……
Geburtsdatum ……/……/……(TT/MM/JJJJ)
Weiblich(w)/männlich(m) ……

Behandlungsgruppe: orale Einnahme (Tabletten)

Hinweise für die Terminplanung:

Orale Einnahme der Medikamente

Das Studienzentrum stellt der Arztpraxis die fertig befüllten und initialisierten Blister zur Verfügung. In der Arztpraxis ist der Medikamentenblister mit der Patientenidentifikation (Name, Vorname, Geburtsdatum bzw. Patientenetikette) zu versehen. Dessen Verwendung ist dem Patienten zu erläutern und die erste Dosis in der Arztpraxis zu entnehmen. Anschliessend nimmt der Patient während der gesamten Studienteilnahme während 28 Tagen die Medikamente selbständig ein (täglich 1 Tablette a 1000 µg Vitamin B12)

Termine im Studienzentrum

Falls Termine im Studienzentrum anfallen, können diese von Mo-Fr von 8.00 – 18.00 h durchgehend eingeplant werden. Termine ausserhalb der Öffnungszeiten sind möglich, müssen aber vorher mündlich abgesprochen werden.

Visit	Datum (TT/MM/JJ)	Zeit (HH:MM)	Wo?	Was?
V7			Arztpraxis	Nächste Blutentnahme
V14			Arztpraxis	Nächste Blutentnahme
V28			Arztpraxis	Letzte Blutentnahme

Bemerkungen
……
……
……

Rückfragen
Bei Rückfragen können Sie gerne sich direkt an das Studienzentrum wenden.

Studienleitung
Corina Metaxas
Pharmaceutical Care Research Group
Universität Basel

Institut für Labormedizin
Kantonsspital Olten
Baslerstrasse 150
4600 Olten
Tel. 062 311 51 01

QD-B1 Vitamin B12 Studie	Besuch 1	Prüfer Initialen	Patient ID
		☐☐	☐☐

T 079 548 47 28

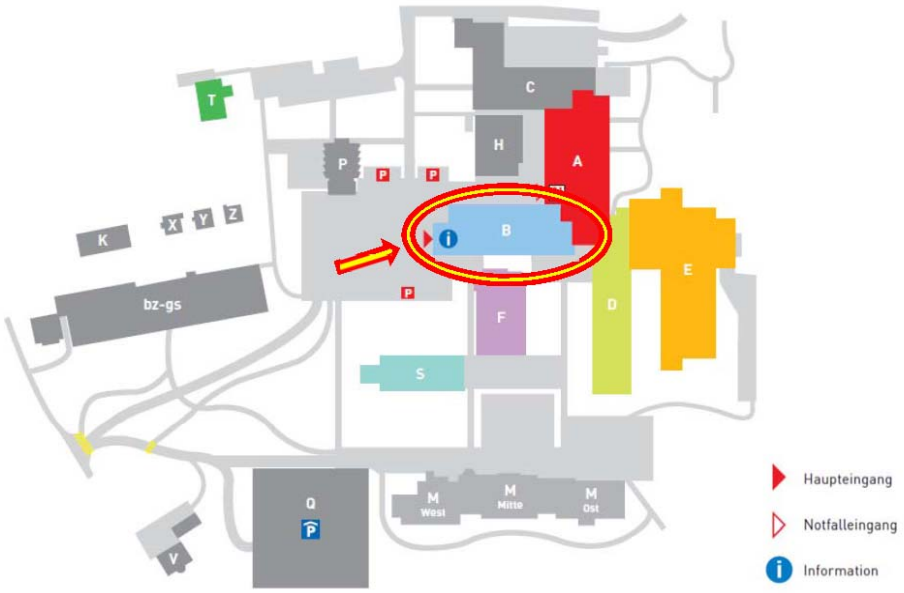
So erreichen Sie uns:

Zu Fuss vom Bahnhof Olten (10 Minuten): Ausgang Stadt benutzen, über die Bahnhofbrücke gehen und dann nach rechts in den Amthausquai (der Aare entlang) biegen, nach 400 Metern links über einen kurzen Waldweg zum Spital (Wegweiser beachten).

Mit öffentlichen Verkehrsmitteln vom Bahnhof (5 Minuten): Ausgang Stadt benutzen und mit dem Bus Linie 2 (Richtung Trimbach) bis Haltestelle Kantonsspital fahren.

Mit dem Auto: In Olten Richtung Trimbach/Basel fahren. Das Spital befindet sich 500 Meter vom Stadtzentrum entfernt auf der rechten Seite. Gebührenpflichtige Parkzonen vorhanden.

Die Blutentnahmen finden im ersten Stock des markierten Gebäudes (Haupteingang) im Kantonsspital Olten statt. Bei der Information wird man Ihnen Auskunft geben, wie Sie das Institut für Labormedizin finden.



Institut für Labormedizin
Kantonsspital Olten

QD-B1 Vitamin B12 Studie	Besuch 1	Prüfer Initialen	Patient ID
		☐☐	☐☐

Baslerstrasse 150
4600 Olten
Tel. 062 311 51 01

Protokoll Baseline Visit (V0)

solothurner spitäler ag

Einschlusskriterien

Ziffer		JA	NEIN
4.1	Datum des Besuchs ☐☐ ☐☐ ☐☐ (TT/MM/JJ) ☐☐ ☐☐ (HH:MM)		
4.2	Liegen die Serumcoblaminwerte aus dem Laborbefund unter 200 p/mol pro Liter?	☐	☐
4.3	Ist die Indikation für eine Vitamin B12 Supplementierung gegeben? *(☞ falls NEIN:: Beschränkung auf Akzeptanzstudie→STOPP)*	☐	☐
4.4	Ist die sprachliche Verständigungsmöglichkeit für die Studienteilnahme ausreichend?	☐	☐
4.5	Patient/-in ist mindestens 18 Jahre alt?	☐	☐
4.6	*Der Patient hat im vorangehenden Monat keine pharmazeutischen Präparate konsumiert, welche Einfluss auf die Vitamin B12 Versorgungslage haben ?*	☐	☐
4.7	*Der Patient hat keine bestehende Diagnose:* • *Diagnostizierte Demenz* • *Transcobolamin Transorter Defekt*	☐	☐
4.8	Liegt die unterzeichnete informierte Einverständniserklärung F_IC vor? *(☞ falls NEIN → Formular unterzeichnen lassen)*	☐	☐
	ⓘ Ziff. 4.2 bis 4.8stellen Einschlusskriterien dar. Ist eine der Fragen 4.2 bis 4.8 nicht mit JA beantwortet, so kann der Patient nicht in die Studie aufgenommen werden.		

Allgemeine Angaben

Ziffer		JA	NEIN
4.9	Wurde der Fragebogen Q-ND vom Patienten ausgefüllt und zurückerhalten? *falls NEIN → Fragebogen jetzt ausfüllen lassen*	☐	☐
4.10	Wurde der Fragebogen Q-A vom Patienten ausgefüllt und zurückerhalten? *falls NEIN → Fragebogen jetzt ausfüllen lassen*	☐	☐
4.11	Wurde das Formular F_MV ausgefüllt und mit dem Patienten ergänzt?	☐	☐

Instruktionen

Ziffer		JA	NEIN
4.12	Die Baseline Blutprobe konnte entnommen werden? Datum: ☐☐ ☐☐ ☐☐ (TT/MM/JJ) Zeit: ☐☐ ☐☐ (HH:MM)	☐	☐
4.13	Das Medikationsset wurde abgegeben und erklärt	☐	☐
4.14	Die gemäss Studienprotokoll erforderlichen Termine für die nächsten konnten mit dem Patienten vereinbart werden?	☐	☐
4.15	Bitte stellen sie folgende Unterlagen für das Studienzentrum zusammen(Versand Pat_V0): • Unterzeichnete Einverständniserklärung (Original) • Fragebogen Q-ND • Fragebogen Q-A • Formular F-MV • Blutprobe B_0 • Kopie: beide Seiten des Studienprotokolls: Baseline VisitV0	☐	☐

QD-B1 Vitamin B12 Studie	Besuch 1	Prüfer Initialen	Patient ID
		☐☐	☐☐

Bestätigung des ausführenden Mitarbeiters, dass die Schritte in Ziff.4.1 bis 4.15 wie vorgesehen durchgeführt werden konnten:

Datum: ☐☐ ☐☐ ☐☐ (TT/MM/JJ) Visum:

Studienprotokoll: Visits V_7 bis V_28

Bitte protokollieren Sie bei jeden Visit die zugehörigen Spalten in der Tabelle:

Visit		JA	NEIN
V7	Datum des Besuchs ☐☐/☐☐ ☐☐ (TT/MM/JJ)		
	Der Visit wurde termingerecht wahrgenommen? (☞ *falls NEIN → Bitte unter Bemerkungen notieren)*	☐	☐
	Zeitpunkt der Blutentnahme ☐☐ ☐☐ (HH:MM)		
	Fragebogen Q_A_7 wurde vom Patienten ausgefüllt und zurückerhalten?	☐	☐
	Visum Mitarbeiter : ……		
V14	Datum des Besuchs ☐☐/☐☐ ☐☐ (TT/MM/JJ)		
	Der Visit wurde termingerecht wahrgenommen? (☞ *falls NEIN → Bitte unter Bemerkungen notieren)*	☐	☐
	Zeitpunkt der Blutentnahme ☐☐ ☐☐ (HH:MM)		
	Der leere Pharmisblister wurde zurückerhalten?	☐	☐
	Der neue Pharmisblister mit den Tabletten für die nächsten 2 Wochen wurde abgegeben?	☐	☐
	Fragebogen Q_A_14 wurde vom Patienten ausgefüllt und zurückerhalten?	☐	☐
	Visum Mitarbeiter : ……		
V28	Datum des Besuchs ☐☐ ☐☐ ☐☐ (TT/MM/JJ)		
	Der Visit wurde termingerecht wahrgenommen? (☞ *falls NEIN → Bitte unter Bemerkungen notieren)*	☐	☐
	Zeitpunkt der Blutentnahme ☐☐ ☐☐ (HH:MM)		
	Der gebrauchte Pharmisblister wurde vom Patienten zurückerhalten und eingelesen?	☐	☐
	Fragebogen Q_A_28 wurde vom Patienten ausgefüllt und zurückerhalten?	☐	☐
	Fragebogen F-MV wurde nochmals mit dem Patienten besprochen und falls nötig ergänzt?	☐	☐
	Visum Mitarbeiter : ……		

Bemerkungen:

……
……
……
……
……
……

KANTON AARGAU

Departement
Gesundheit und Soziales
Kantonale Ethikkommission

Formular für die Beschlussmitteilung der Kantonalen Ethikkommission

Die **Kantonale Ethikkommission** Aargau des Departementes Gesundheit und Soziales hat an ihrer Sitzung vom **25. Juni 2009** gestützt auf die Verwaltungsvereinbarung zwischen den Kantonen Aargau und Solothurn vom 16. November 2005 sowie die einschlägigen Bundesgesetze (in der Zusammensetzung, wie sie nachstehend wiedergegeben ist) das folgende Forschungsprojekt eingehend begutachtet.

Forschungsprojektes Ref.Nr. EK: 2009/041

Aspirin- und Clopidogrelresistenz:
Non-Compliance und andere dazu beitragende Faktoren

Prüfer/in (verantwortliche Studienleiter/in am Versuchsstandort)

Name, Vorname, Titel:	Philipp Walter, dipl. pharm.
Funktion:	Leiter Med. Labor Olten MLO AG
Adresse:	Frohheimweg 12 - 4600 Olten

Die Ethikkommission stützt ihre Beurteilung auf die Unterlagen, wie sie dem beiliegenden „Basisformular zur Einreichung eines biomedizinischen Forschungsprojektes" vom 2. Juni 2009 beigefügt sind.

☒ normales Verfahren ☐ vereinfachtes Verfahren ☐ Nachbegutachtung

Die Ethikkommission kommt zu folgendem **Beschluss**:

☐ **A positiv**
☒ **B positiv mit Empfehlungen** (siehe Seite 2ff)
☐ **C positiv mit Auflagen** (siehe Seite 2ff)
Nachbegutachtung durch KEK notwendig ☐
schriftliche Mitteilung an Ethikkommission ausreichend ☐
☐ **D negativ (mit Begründung und Erläuterung für die Neubeurteilung)** (siehe Seite 2ff)
☐ **E Nicht-Eintreten (mit Begründung)** (siehe Seite 2ff)
☐ **F Bewilligung "Departement Gesundheit und Soziales" ist erforderlich**
☐ **G Die Studie wurde zurückgezogen**

Der Beschluss gilt auch für die im "Basisformular" gemeldeten weiteren Prüfer/innen im Zuständigkeitsbereich der Ethikkommission.

Ref. Nummer KEK 2009/041

Empfehlungen
Patienteninformation
- Auf Seite 3/3 sollen die Angaben von Herrn PD Dr. Hersberger gestrichen werden.

Einverständniserklärung
- In der Rubrik "Prüfärztin/Prüfarzt" soll nur Herr Dr. Romanens aufgeführt werden. Herr PD Dr. Hersberger ist zu streichen.
- Die Einverständniserklärung sollte mit folgendem Satz ergänzt werden: Ich bin damit einverstanden, dass die Resultate meinem behandelnden Arzt zugestellt werden.
- Es soll unter dem Titel "Unabhängige Befragung" ein weiterer Punkt aufgeführt werden bezüglich der Folgestudie im Sinne von "Ich bin damit einverstanden, dass man mich zu einem späteren Zeitpunkt wieder kontaktiert und mich anfragt, ob ich an einer Folgestudie teilnehmen möchte oder nicht (mit Ja/Nein-Kästchen darstellen).
- Falls Daten ins Ausland gehen, muss dies Bestandteil der Patienteninformation sowie der Einverständniserklärung sein.

Bitte jeweils die Änderungen in den revidierten Dokumenten markieren. Die Bearbeitung wird dadurch erleichtert und kann schneller erfolgen. Besten Dank !

Ref. Nr. 2009/041

Zusammensetzung der Ethikkommission
Die Ethikkommission tagte in der nachfolgend erwähnten Zusammensetzung und war damit beschlussfähig (Art. 32 der Verordnung über klinische Versuche mit Heilmitteln vom 17. 10. 2001).

					am Beschluss beteiligt	
	Name, Vorname	**Berufliche Stellung / Titel**	m	f	**ja**	**nein**
Vorsitz	Dorina Jerosch	Vizepräsidentin, lic. iur. Juristin RD, DGS	☐	☒	☒	☐
Mitglieder	Edith Saner	Leiterin Bildung und Beratung, Dipl. Pflegefachfrau	☐	☒	☒	☐
	Reinhard Hauswirth	Facharzt für Allgemeinmedizin, Dr. med.	☒	☐	☒	☐
	Peter Bachmann	Facharzt für Kinder/Jugendpsychiatrie, Dr. med.	☒	☐	☒	☐
	Roland Schoenenberger	Facharzt für Innere Medizin/Intensivmedizin, Prof. Dr. med.	☒	☐	☒	☐
	Judith Seitz	Fachärztin für Allgemeinmedizin	☐	☒	☒	☐
	Martin Schaufelberger	Spitalseelsorger	☒	☐	☒	☐
für Biometrie zuständiges Mitglied	Dr. Hauswirth		☒	☐	☒	☐

Pro Memoria: **Pflichten des/der verantwortlichen Prüfers/in**
- Geprüfte Produkte und Vergleichsprodukte (Arzneimittel und Medizinalprodukte) müssen - zur Sicherstellung der Qualität und der Sicherheit - fachgerecht hergestellt, evaluiert und eingesetzt werden.
- Meldepflicht bei: a) schwerwiegenden unerwünschten Ereignissen (serious adverse events) unverzüglich
  b) neuen Erkenntnissen, die während des Versuchs verfügbar werden und die Sicherheit der Versuchspersonen sowie die Weiterführung des Versuchs beeinflussen können
  c) Änderung des Protokolls (Versuchsplans)
  d) Ende oder Abbruch der Studie
- Zwischenbericht: einmal pro Jahr
- Meldungs- oder Bewilligungspflicht von Studien bei Swissmedic bzw. anderen Bundes- oder kantonalen Behörden (bei sponsorisierten Studien ist dies die Pflicht des Sponsors)
- Schlussbericht

Gebühren: 2'500.-

(Die Gebührenerhebung für die Nachbegutachtung von Forschungsuntersuchungen, Ergänzungen/Amendments bleibt ausdrücklich vorbehalten und richtet sich nach § 4a Abs. 1 lit. b) Gebührenverordnung)

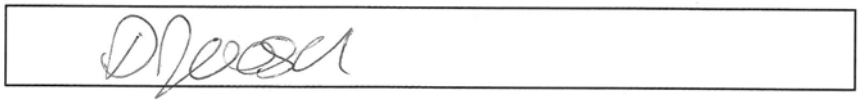
Die Gebührenerhebung richtet sich nach § 4a Abs. 1 lit. a) der Verordnung über die Gebühren in den Bereichen Gesundheit, Soziales und Zivilschutz (Gebührenverordnung) vom 10.6.1991 (Stand 1.10.2005).

Für die Ethikkommission:

Ort, Datum: Aarau, 30. Juni 2009

Name: Dorina Jerosch, lic. iur., Vizepräsidentin

Unterschrift(en):



Swissmedic/BAG/SA
MW 1.1.2002

Departement Pharmazeutische Wissenschaften
Pharmaceutical Care Research Group
Tel. 062 205 60 36
Fax. 062 205 60 39
philipp.walter@unibas.ch
www.pharmacare.unibas.ch

QD-QP3

Ihre Meinung zur Therapie mit Medikamenten

BMQ: Believes about Medicines Questionnaire

Gerne würden wir Ihre **persönliche Überzeugung** in Bezug auf Medikamente, die Sie aufgrund Ihrer Krankheit einnehmen, wissen.

Dabei präsentieren wir Ihnen **10 Meinungsäusserungen** von verschiedenen Patienten. Bitte kreuzen Sie jenes Kästchen an, welches Ihrer Meinung am ehesten entspricht.

Es existieren keine richtigen/falschen Antworten. Nur Ihre persönliche Sicht interessiert uns.

	Den untenstehenden Aussagen 1-10 stimme ich...	voll und ganz zu 5 ++	eher zu 4 +	weder noch zu 3 +-	Eher nicht zu 2 -	über-haupt nicht zu 1 --
1.	Meine derzeitige Gesundheit hängt von meinen Medikamenten ab.	☐	☐	☐	☐	☐
2.	Es bereitet mir Sorgen, Medikamente nehmen zu müssen.	☐	☐	☐	☐	☐
3.	Mein Leben, so wie ich es jetzt führe, wäre ohne meine Medikamente nicht möglich.	☐	☐	☐	☐	☐
4.	Ohne meine Medikamente wäre ich sehr krank.	☐	☐	☐	☐	☐
5.	Manchmal mache ich mir Sorgen wegen der langfristigen Auswirkungen meiner Medikamente.	☐	☐	☐	☐	☐
6.	Meine Medikamente sind mir ein Rätsel.	☐	☐	☐	☐	☐
7.	Meine zukünftige Gesundheit hängt von meinen Medikamenten ab.	☐	☐	☐	☐	☐
8.	Meine Medikamente stören mein Leben.	☐	☐	☐	☐	☐
9.	Manchmal mache ich mir Sorgen, zu abhängig zu werden von meinen Medikamenten.	☐	☐	☐	☐	☐
10	Meine Medikamente schützen mich davor, dass es mir schlechter geht.	☐	☐	☐	☐	☐