Drug Resistance with Monitored Adherence

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To my friends at Bahnhofstrasse, Aarau (2006 – 2012)

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ABBREVIATIONS

ACE-ME	Assessment, Collaboration, Education, Monitoring and Evaluation
ADP	Adenosin diphosphate
AHT	Antihypertensive therapy
ANOVA	Analysis of Variance
(A)U	(Arbitrary) Unit
AUC	Area under the Curve
BD	Becton Dickinson
BMI	Body mass index
BMQ	Beliefs about Medicines Questionnaire
CI	Confidence intervals
CIOMS	Council for International Organizations of Medical Sciences
COX-1	Cyclooxygenase 1
CV	Coefficient of variation
CYP	Cytochrome P_{450}
DBP	Diastolic blood pressure
DDI	Drug drug Interaction
DOT	Directly observed therapy
e-MCM	electronic Multidrug Compliance Monitoring
ECMD	Electronic compliance monitoring devices
EMA	European Medicines Agency
ESC	European Society of Cardiology
ESCP	European Society of Clinical Pharmacy
FDA	United States Food and Drug Administration
GP	General Practitioner
HDL-C	High density lipoprotein cholesterol
Her-2/neu	Human epidermal growth factor receptor 2
h:min:sec	Hours:minutes:seconds
HLA	Human leucocyte antigen
holoTc	Holotranscobolamin
hcy	Homocystein
i.m.	Intramuscular
IAS	International Arteriosclerosis Society
IMP	Investigational Medicinal Product

ICH-GCP	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use – Good Clinical Practice
LDL-C	Low density lipoprotein
LLD	Lipid lowering drug
LMT	Lipid modifying therapy
LSD	Least significant difference
LTA	Light transmission assay
MCV	Mean cell volume
MDR1	Multidrug resistance gene
MEA	Multiple electrode aggregometry
MeSH	Medical Subject Heading
MEMS®	Medication Event Monitoring System®
MGMM	Measurement-guided medication management
MMA	Methylmalonic acid
MMAS	Morisky Medication Adherence Scale
OTC	Over-the-counter drugs
PAOD	Peripheral arterial occlusive disease
PCNE	Pharmaceutical Care Network Europe
POEMS	Polymedication electronic monitoring system
PFA	Platelet function analyser
PPI	Proton pump inhibitor
Rx	Prescription drugs
SAE	Sudden Adverse Event
SBP	Systolic blood pressure
SD	Standard deviation
SGAM	Swiss Society of General Medicine
SGIM	Swiss Society of General Internal Medicine
SMS	Short Messaging System
SPSS®	Statistical Package for the Social Sciences®
SSPhS	Swiss Society of Pharmaceutical Sciences
SSCC	Swiss Society of Clinical Chemistry
SUSAR	Suspected unexpected serious adverse reaction
TC	Total cholesterol
TG	Triglycerides
t_{VAR}	Time variability of drug intake
TXB2	Thromboxane B2

US	United States of America
VB12	Vitamin B_{12}
VASP	Vasodilator stimulated phosphoprotein
Wonca	World organization of national colleges, academies and academic associations of general practitioners / family physicians

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SUMMARY

Drug resistance can be defined as the failure of a drug to exert its expected effect on pharmacological biomarkers. Resistance is an inherent challenge to pharmacotherapy with treatments that are generally considered as safe and effective. Limited effectiveness in specific patient subgroups can result from a broad spectrum of factors, which can be classified into pharmaco-genetic, cellular and clinical factors. However, drug response in daily life is the result of the interplay between numerous contributors. Thus, studying the impact of certain factors is of limited value if others are not controlled for.

Non-adherence in outpatient treatment is common and constitutes a major challenge to translate drug efficacy known from controlled conditions in clinical trials into daily life effectiveness. Drug resistance and the lack of biomarker target achievement in chronic outpatient treatment is likely to be confounded by non-adherence rather than being a simple function of pharmaco-genetic factors. Drug drug interactions constitute another clinical factor that may add to the challenge of drug resistance. Both non-adherence and exposure to drug drug interactions can be controlled for by the application of a new technology for adherence monitoring that was developed in the framework of this thesis.

Personalised medicine aims at tailoring drug treatments to specific patient subgroups. Additionally to biomarker characteristics of a patient, factors affecting the patient's ability to adhere to a certain regimen should be considered when analysing inter-individual variability of drug response. Interventions to overcome drug resistance must incorporate any of the identified factors when effectiveness and toxicity of outpatient therapy should be optimized by a truly personalised approach.

It was the aim of this thesis to apply this multifactorial model of drug resistance to cardiovascular medication in outpatients. A special focus was set on antiplatelet therapy with aspirin and clopidogrel, for which a prospective study with the application of multidrug adherence monitoring was designed and executed. In a second prospective study aimed at comparing effectiveness of oral vitamin B_{12} substitution in comparison to intramuscular injections, the adherence monitoring technique should be employed to track adherence to a single drug.

In **project A**, we studied the prevalence of unreached biomarker targets in patients with lipid-lowering drugs (LLD) and antihypertensive drugs (AHT). For this investigation, a retrospective analysis of data that was collected in a population-based cross sectional study with 4380 patients was performed. Of 863 patients that were treated with lipid lowering

and/or antihypertensive drugs, 306 (35.5%) did not reach the respective therapeutic with at least one of the treatments. The rates of missed target attainment were 25.8% (LLD) and 36.3% (AHT). These impressive rates may serve as estimates of the burden of drug resistance in an unselected outpatient population. According to the multifactorial model of drug resistance, disease factors, clinical and pharmaco-genetic factors are presumed contributors. Patients with concomitant prescription of LLD and AHT were significantly less likely to miss their biomarker targets in both treatments. This may be due to optimised adherence and disease awareness in patients that were prescribed both treatments and certainly underscores the need to involve clinical factors when investigating factors to resistance.

Consequently, a prospective study on antiplatelet resistance involving multidrug adherence monitoring was designed in **project B**. Within this project, the polymedication adherence monitoring system (POEMS) was developed, which aimed at monitoring of the patient's adherence to all his oral solid drugs. This study should be the first to allow evaluating the impact of drug drug interactions, pharmaco-genetic polymorphisms and disease factors under prospectively measured objective adherence in chronic antiplatelet therapy. The study was approved by the ethics committee of Aargau and Solothurn, Switzerland and was executed between June 2010 and July 2011 in Olten, Switzerland.

The results of the study were analysed and worked up in the projects C and D. In **project C1**, the pattern of timing adherence of the patients that were included in the parent study on antiplatelet resistance was analysed. The polymedication electronic monitoring system proved to be a suitable tool to collect comprehensive data on multidrug adherence and allowed identifying 7:41 h, 12:09 h and 18:36 h as median intake times of the morning, midday and evening doses. Significant delays of the morning drug intake times were observed on Saturday and Sunday, and the time variability of drug intake was generally lower in the morning than in the evening. A tendency towards lower LDL-C values in patients with a lower time variability of the lipid lowering drug (LLD) containing dose was observed, suggesting that effectiveness of LLD may depend on the precision of timing adherence. Subjective adherence measures such as the scores calculated from the Believes about Medicines Questionnaire (BMQ) and the Morisky Medication Adherence Scale (MMAS-8) were neither associated with objective adherence parameters nor predictive of LDL-C levels in patients with lipid lowering therapy. In **project C2**, the use of POEMS was demonstrated in an exemplary case of a patient whose irrational timing adherence could be disclosed and partly corrected by the intervention of a pharmacist.

In **project D**, the results of the main study on antiplatelet resistance with aspirin and clopidogrel were evaluated. The evaluable patients (N=82) were analyzed separately in two overlapping samples of 69 aspirin users and 32 clopidogrel users. After adherence monitoring, resistance was found in 20% of the aspirin users and 25% of the clopidogrel users. Non-adherence was dismissed as a major contributor to drug resistance with aspirin and clopidogrel in chronic outpatient treatment due to the absence of significant differences of platelet aggregation before and after adherence monitoring. Multidrug adherence monitoring with POEMS allowed to precisely measuring the exposure to drug drug interactions (DDIs). Actual exposure to DDIs was lower than when referring to prescription data. The consideration of data from multidrug adherence when analyzing the impact of DDIs prevented from misleading results due to dilution effects by non-adherence to interfering drugs. The potential DDI of clopidogrel with high-dose lipophilic statins was found probable and may result in significant effects when analyzing a higher number of patients. Statistically significant effects on aspirin resistance were found for diabetes mellitus and systemic inflammation. These disease factors were also most probable to have an impact on antiplatelet resistance with clopidogrel, while the impact of CYP2C19 polymorphism on antiplatelet resistance seemed negligible.

The consideration of adherence as an independent variable when studying resistance or response to oral drug therapy has further been implemented in **project E**, which aimed at demonstrating the non-inferiority of oral high-dose vitamin B_{12} substitution in comparison to intramuscular injections. Other than in the previous project with multidrug adherence monitoring, POEMS was planned to be employed for tracking adherence with oral vitamin B_{12} only. The study to compare oral and i.m. substitution of vitamin B_{12} has been approved by the ethics committee of Aargau and Solothurn, Switzerland and was successfully notified by Swissmedic, the Swiss agency for therapeutic products in March 2012. This study will be executed outside of this thesis.

In conclusion this thesis showed that the investigation of antiplatelet resistance by the application of this unique approach with prospective adherence monitoring to all oral solid drugs is feasible. We were able to characterise the temporal pattern of drug intake and found associations between the timing variability of drug intake and attained LDL-C levels in patients with lipid lowering therapy. In antiplatelet therapy with aspirin and clopidogrel, resistance rates of 20% and 25% could be confirmed despite prospective adherence monitoring. POEMS allowed to assess the precise exposure to DDIs and to analyse the timing effect of the DDI between clopidogrel and lipophilic statins. The results that were

found with this methodology supported staggered versus concomitant intake of these potentially interfering drugs.

The following conclusions could be drawn:

- The POEMS technology allowed collecting data on multidrug timing adherence which has not been reported before.
- The new technology and procedures were well accepted by the patients.
- Objectively measured timing adherence parameters are suitable to describe intake characteristics of a patient. Significant deviations from prescribed drug intake can be observed, and intake characteristics vary in different patients' groups.
- The combination of the weekly multidrug blister together with the electronic adherence monitoring was effective to rule out non-adherence.
- The association between the time variability of the LLD intake and LDL-C levels suggests an impact of timing adherence on statin effectiveness.
- Antiplatelet resistance in outpatients with maintenance doses of aspirin and clopidogrel is common. Approximately 20% of patients with aspirin and 25% of the patients with clopidogrel are affected.
- Aspirin resistance as measured with the MULTIPLATE® analyser is rather a dichotomous phenomenon, while platelet aggregation with clopidogrel is a continuous measure.

Our recommendations for daily practice are:

- If there is doubt about the effectiveness of the treatment with aspirin or clopidogrel, the investigation by specific in vitro platelet aggregation tests is recommended. If the test result does not comply with the expected inhibition of platelet aggregation, the further investigation should involve multidrug adherence monitoring to rule out non-adherence and to measure the exposure to potentially interfering drugs. If the insufficient inhibition of platelets persists after one week of multidrug adherence monitoring, measures should be taken to optimize antiplatelet therapy. In the case of clopidogrel, CYP2C19 genotyping should be part of the workup. Comprehensive consideration of the test results, together with medication and clinical data should allow finding alternative treatments to prevent the patient from the potential clinical consequences of antiplatelet drug resistance.
- Multidrug adherence measurement may serve as a useful diagnostic tool to disclose the timing adherence pattern of polymedicated patients. The adherence report is

useful to visualize the adherence pattern and may serve as a useful background to discuss timing adherence issues together with the patient.

1. GENERAL INTRODUCTION

1.1. DRUG RESISTANCE

The term "drug resistance" has been most commonly applied for antimicrobial drugs, where it is used to describe the ability of the pathogen to emerge from the antibiotic pressure due to the development of specific mechanisms of resistance. A broader definition involves the failure of any drug to exert its expected measurable effect on the treated subject, irrespective of the cause. Other than "treatment failure", which is used to address clinical outcomes, drug resistance refers to an intermediate outcome which can notably be measured with a biomarker that is predictive of the drug's effectiveness.

This broader definition of drug resistance has been the background of its application in various fields of drug therapy. Drug resistance has become a key issue in cancer therapy, but has also found application in the pharmacologic treatment of epilepsy, hypertension or depression, just to name a few examples [1-4]. Incomparable attention has been attracted by the phenomenon of antiplatelet drug resistance, which has mainly been nourished by the scientific debate on clopidogrel response variability and the contribution of pharmaco-genetic factors [5].

The underlying causes for drug resistance are numerous and reach from clinical (e.g. patient non-adherence) to pharmaco-genetic (e.g. polymorphic expression of drug targets) contributors. Their impact on resistance varies widely and depends on the pharmacological properties of the drug. In many cases, resistance is rather a gradual phenomenon which is reflected by a continuous measure, for which the binary categorisation into "resistant" and "responder" is an unjustified oversimplification. In the area of personalised medicine, the factors associated with drug resistance should be identified and concepts to overcome the negative outcomes associated with drug resistance should be developed to guide patients and their caregivers to rational and evidence based optimization of the implemented drug therapies.

1.1.1. ANTIPLATELET DRUG RESISTANCE

Aspirin has been used for the prevention and treatment of thrombosis for many years and offers an approximately 25% reduction for stroke, myocardial infarction, and cardiovascular death [6]. The mechanism of its antiplatelet effects has first been described in 1971 [7]. Other antiplatelet agents such as cilostazol and later ticlopidine have been introduced. The newer area of antiplatelet agents has mainly been shaped by the ADP receptor antagonist clopidogrel since it has been approved by the FDA in 1997 and received extended approval

in 2002 for primary cardiovascular prevention. These approvals were later confirmed by the European drug authorities. The inhibitory effect of clopidogrel and other antiplatelet agents can be quantified with *in vitro* assays (see Table 1). The historical standard has been set by a method that used light transmittance through platelet rich plasma after inducing platelet aggregation with arachidonic acid, ADP, collagen and other activators [8]. In the past years, new assays to measure the effects of antiplatelet medication have become commercially available.

Table 1. Commercially available assays to measure in vitro effects of aspirin and clopidogrel, modified from [9].

Assay	Measure	Sample
Light transmission assay (LTA)	Decline of light transmittance when platelet aggregation is induced by activators	Platelet rich plasma
Platelet count (conventional hematology analyser)	Platelet count after induction of aggregation	Whole blood
Impedance aggregometry MULTIPLATE®	Impedance between electrodes after addition of platelet aggregation inducers	Whole blood
PFA-100® (Siemens)	Time until the blood sample flow through an activator-coated cell stops	Whole blood
Vasodilator stimulated phosphoprotein (VASP) flow cytometry assay	Inhibition of P_2Y_{12}-mediated VASP phosphorylation	Whole blood
Ultegra® Rapid Platelet Function Assay / VerifyNow®	Reduction of light transmittance by agglutination of fibrinogen-coated beads	Whole blood
Cone and Plate analyser (CPA)	Platelet adhesion and aggregation under laminar flow with uniform high shear.	Whole blood
Thrombelastography (TEG)	Prolonged clot formation	Whole blood
Thromboxan B_2 (TXB2 (Aspirin only)	Decline in TXB_2 formation (by inhibition of COX-1)	Serum
11-dehydrothromboxane B_2 (Aspirin only)	Decline in TXB_2 formation and excretion (by inhibition of COX-1)	Urine

An inter-individual variability of antiplatelet response has not only been described for clopidogrel, but could also been found to a lower degree in aspirin users [10]. Despite the proven efficacy of low-dose aspirin in cardiovascular prevention, there have always been patients who experienced clinical events despite antiplatelet therapy. Antiplatelet resistance with aspirin constituted a plausible background. Predictive *in vitro* tests and knowledge of associated factors are helpful for the identification and characterisation of antiplatelet resistance.

1.1.2. CONTRIBUTING FACTORS TO DRUG RESISTANCE

Multiple factors can hinder the drug from inducing the expected response in the treated subject. The impact of different factors depends on the pharmacological properties of the drug, the route of administration, the therapeutic setting and the characteristics of the treated patients. The contributors to antiplatelet drug resistance have been systematically categorised into clinical, genetic and cellular factors [11]. Clinical factors involve inadequate prescribing, patient non-adherence, DDIs and intrinsic factors of the underlying disease. Genetic factors involve pharmacokinetic or pharmaco-dynamic polymorphisms, whereas cellular factors modulate response to treatment by receptor up- or down regulation and variation of enzyme activity. The contributing factors to resistance for the illustrative cases of aspirin (figure 1) and clopidogrel (figure 2) are depicted below.

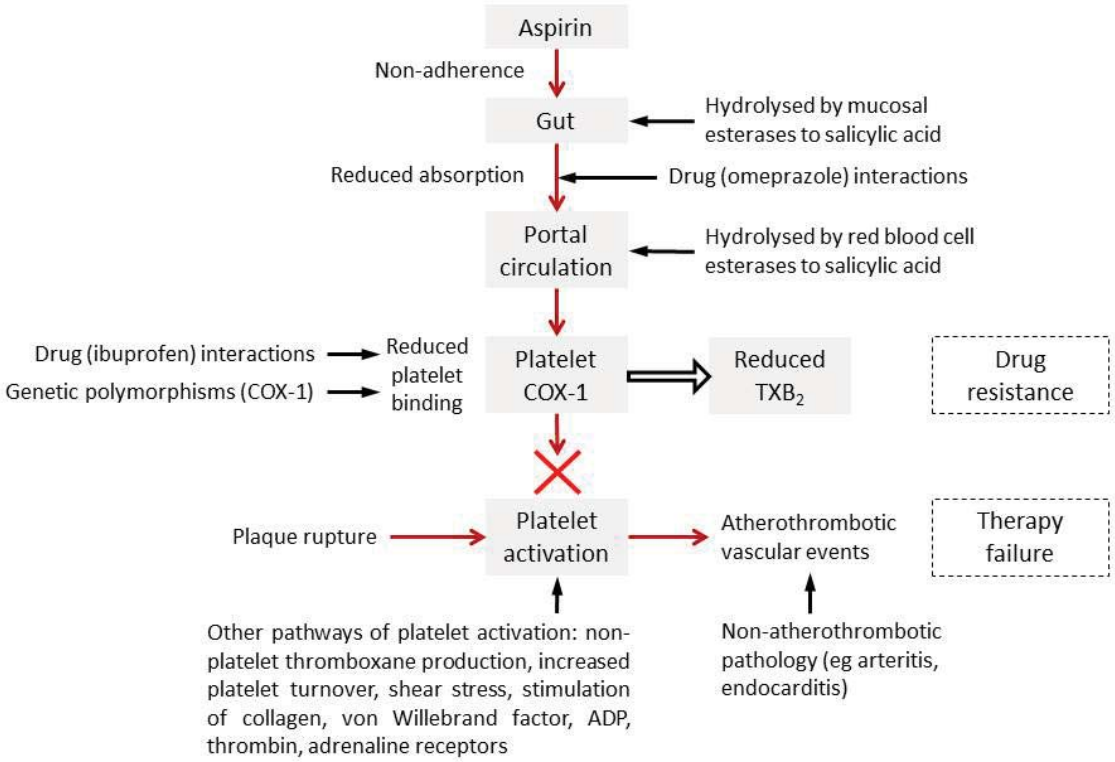

Figure 1. Proposed mechanisms of aspirin resistance (modified from [12]).

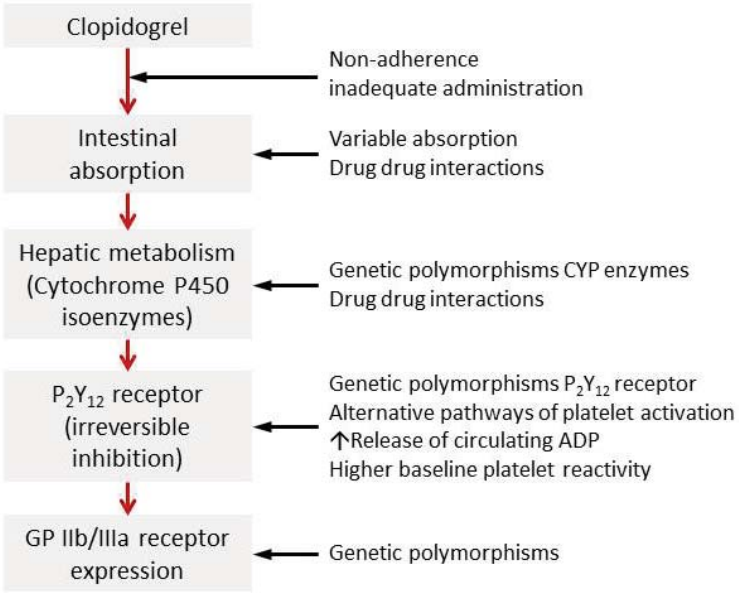

Figure 2. Proposed mechanisms of the response variability with clopidogrel (adapted from [13]). GP indicates glycoprotein.

1.2. PHARMACOLOGICAL BIOMARKERS

The introduction of the term "pharmacological biomarker" in 2008 in the MeSH terminology reflected the ongoing trend towards biomarker-based pharmacological concepts in the light of drug treatment personalisation. According to the MeSH definition, the term "pharmacological biomarker" refers to a "measurable biological parameter that serves for drug development, safety and dosing (drug monitoring)". Biological markers or, more commonly, biomarkers are "quantifiable biological parameters which serve as health- and physiology-related assessments, such as disease risk, (…), environmental exposure and its effects …"[14].

Some biomarkers like Her-2/*neu* (overexpression in breast cancer associated with response to trastuzumab), HLA-B*51 (abacavir hypersensitivity) and HLA-A*3101 (carbamazepine toxicity) successfully translated from basic science into clinical routine. They help to predict safety and efficacy of the application of specific drugs in distinct patients and thus select the right treatment for each patient [15-17]. Additionally, pharmacological biomarkers for the phenotypical assessment of treatment response may help to optimize dosing and thus contribute to the personalisation of the therapy.

The requirements concerning pharmacological biomarkers have been reviewed by Puntmann [18]. Examples of reliable and clinical biomarkers in general medicine are rare. Low-density lipoprotein cholesterol (LDL-C) to evaluate effectiveness of lipid lowering treatment with

statins is one of the most popular examples. *In vitro* platelet inhibition induced by antiplatelet drugs is another example of a biomarker that could be used for the evaluation of response in clinical practice. Historically, the inhibitory effects of aspirin and clopidogrel have not been routinely monitored. In the meantime, many studies have underlined the clinically predictive value of test results obtained with more recently introduced platelet aggregation assays [19-21]. Many questions, especially regarding the standardisation of antiplatelet test results remained. However, pharmacological biomarkers have the potential to play an important role in the personalisation of antiplatelet therapy because of their ability to provide a rational basis in response-guided interventions [22].

1.3. PERSONALISED MEDICINE

The aim of personalised medicine is to optimize effectiveness and to reduce toxicity of the treatment by tailoring a patients' pharmacotherapy to individual factors that are known to influence the response to treatment. There is no consensus definition of personalised medicine, and experts in the field summarise a diversity of concepts under the term [23]. In a narrow sense, personalised medicine refers to pharmaco-genetic predictors of treatment response. Given the many clinical factors that interfere with the prediction of response and toxicity from genetic factors, personalised medicine should integrate clinical factors in order to bring out the true predictive power of a biomarker in a patient cohort. The patients' clinical background as well as his perception of the disease and its treatment result in a large variation of subjective and objective adherence parameters and, accordingly, to a considerable variability of drug exposure. Subsequently, patient adherence is an important measure to be recorded and analysed to reach further advances in truly personalised medicine. The logical consequence for this thesis was to combine the assessment of pharmacological biomarkers with the objective measurement of multidrug adherence.

1.4. ADHERENCE

According to a new taxonomy introduced by Vrijens et al., "adherence to medications is the process by which patients take their medication as prescribed and which is further divided into three phases: initiation, implementation and discontinuation" [24]. Initiation and discontinuation of treatment are described as "inherently discontinuous actions, whereas implementation of the dosing regimen is continuous", which "precludes a single, quantitatively useful parameter to cover all three" [24]. In the context of this thesis, the focus lies on on-going long-term therapies to be traced over a relatively short time period. Thus we deal mainly with methods to measure and report data on the implementation of the

drug therapy. This is mostly done by comparing the two time-series of the prescribed dosing regimen and the patient's drug dosing history. Other summary parameters which were mainly applied in this thesis describe the intake times, dose-to-dose intervals and the intra-individual variation of drug intake [25]. Adherence has been shown to be an important independent predictor of therapeutic efficacy on cardiovascular outcomes [26]. At least ten types of non-adherence are known, and all of them are associated with specific risks of adverse outcomes, either by the absence of the drug effect or by rebound effects due to drug withdrawal.

Taking Adherence and Timing Adherence

Reported adherence in conventional studies relies basically on taking adherence, which can be calculated from various measures, but mostly rely i) on pill counts or ii) on the medication possession ratio and iii) days covered based on prescription refill data [27]. These measures may be reliable for some situations, but are likely to mostly over-, but sometimes underestimate adherence. Today, a genuine, but pharmacologically naïve cut-off of 80% is often used to interpret data on taking adherence [28]. Data on timing adherence of all oral solid drugs will allow a more sophisticated interpretation of adherence data which involves the pharmacological properties of a drug.

However, the focus of this thesis lies in the precise assessment of timing adherence. Timing adherence should be interpreted in the light of the specific requirements of the prescribed drug. The pharmacological properties of a drug define its forgiveness and thus the requirements regarding the precision in the execution of a therapy plan. Measuring timing adherence is essential to explore whether the patients intake characteristics fulfil the requirements of the prescribed regimen. Relevant deviations in timing adherence would translate into changes of biomarker measurements. The parallel measurement of timing adherence and pharmacological biomarkers is thus helpful to estimate tolerable deviations of timing adherence. Such estimations based on adherence and biomarker data would represent a step towards operational definitions for the implementation of a dosing regimen. Various authors claimed for disease- and drug-specific definitions that indicate clinically relevant deviations from the prescribed medication regimen [29-31].

Intentional and Unintentional Non-Adherence

Intentional non-adherence results from the patients' decision not to take medication or to take it in a way that differs from the recommendations [32]. Unintentional non-adherence occurs when patients are prevented from implementing their intention to take the

medication as prescribed by factors beyond their control, such as forgetfulness, poor comprehension (e.g. of the drug regimen), or physical inability to manage the medication. The two related types of behaviour may result in different pattern of objectively measured non-adherence, but are typically reflected by differing subjective measures of adherence.

Objective Measures for Adherence Assessment

A multitude of methods has been introduced for the objective measurement of adherence. For example, digoxin and phenobarbital in sub-pharmacological doses have been used as *tracers*. Despite their ability to precisely quantify a certain measure (e.g. drug concentration), there are drawbacks for the interpretation. Drug or tracer concentrations are not capable to give information about the dosing history and are generally not suitable to detect white coat adherence. Thus, the diverse methods differ in their ability to reflect the different forms of non-adherence.

Electronic adherence assessment is an indirect objective measure of adherence. First data with the Medication Electronic Monitoring System (MEMS®) have been reported over 20 years ago [33]. MEMS® was mainly employed in clinical trials and allowed insights into timing adherence characteristics of single drugs and laid the fundamentals for the understanding of drug effectiveness in the ambulatory setting. Specific studies with such adherence assessment have allowed unmasking the impact of non-adherence on effectiveness with antihypertensive drugs [34]. Statistical considerations on adherence as a control variable in multivariate analysis of drug effectiveness have become necessary, because the stringent data clarified that 100% adherence is a presumption that generally overestimates actual frequency of drug intake. Any finding regarding drug efficacy and safety may be diluted by an unknown contribution of non-adherence.

In the past years, several companies have developed commercially available electronic devices to monitor and enhance patient adherence. Beside the simple registration of a time stamp from an event that is associated with drug adherence (e.g. cap removing, blister opening), they give feedback and use modern communication technologies in order to help patients to execute their therapy plan in concordance with their prescriptions.

Polymedication Electronic Monitoring System (POEMS)

Technological progress allowed imprinting electrically conductive ink onto polymer foils. The first clinical experience with this technique has been collected when mapping electronic circuitries on the backside of a commercial drug blister, which allowed tracking adherence with an oral anticoagulant without the need to remove the drug from its primary packaging

[35]. Further development in the context of this thesis allowed adapting the technology to a weekly multidrug blister pack (Pharmis®, Pharmis GmbH, Beinwil am See, Switzerland). This allowed monitoring adherence with the entire oral solid medication of a patient. Beside taking and timing adherence, the exposure to drug drug interactions can be measured. In the context of drug resistance and the assessment of contributing factors, this tool is essential for the quantification of clinical factors as outlined below. Otherwise, only *potential* factors instead of *actual exposure* would be measured.

Subjective Measures of Adherence

Subjective measures to assess adherence have been developed i) to identify patients at risk for non-adherence and ii) to characterise the personal background of non-adherence (intentional, non-intentional, patient beliefs and concerns). Subjective methods are relatively easy to perform and are cheap in comparison to objective methods, but are affected by recall bias. Furthermore, results can be affected by patients who give socially desirable answers. Two established questionnaires were used in the core projects (projects B, C, D) of this thesis:

- The Beliefs about Medicines Questionnaire (BMQ) was developed by Horne and validated in various clinical settings [36]. In brief, it is based on the concept that the patients' adherence is the result of his view of the necessities and concerns of the drug therapy. Sub-scores for necessities and concerns can be calculated, while the BMQ differential score integrates both measures.
- The Morisky Medication Adherence Scale (MMAS-8) has proved to predict adherence in outpatients [37]. The MMAS-8 score is calculated from the patients' answers to 8 questions related to adherence, with lower scores indicating a higher risk of non-adherence.

1.5. SUMMARY OF RATIONALE AND APPROACH

Drug resistance is characterised by the failure of a drug to produce the expected biomarker response in the treated patient. Resistant patients can thus be identified by a relatively simple measure in therapies where biomarkers exist that reflect the drug effect. Biomarker target attainment rates in cross-sectional studies are convenient to give an estimate on the burden of drug resistance with the respective treatment.

In a first retrospective study of unmet biomarker targets in cardiovascular risk patients treated with antihypertensives and lipid lowering drugs, we aimed at estimating the approximate rate of drug resistance with cardiovascular medication in an ambulatory setting.

The following project on antiplatelet resistance represented the core study in the framework of this thesis. Its objective was to go beyond the surface of resistance and to assess the impact of the multiple presumed factors to drug resistance, thereby including prospective electronical adherence-monitoring to all oral solid drugs. Very recently, multidrug adherence monitoring with POEMS was developed which allows to precisely assessing adherence and exposure to DDI, two important clinical factors. Additionally, adherence monitoring with POEMS allows calculating summary statistics of timing adherence as a measure of implementation of the drug regimen.

In a sub-study, we wanted to explore associations between the temporal pattern of multidrug adherence and biomarker response, which is a representative measure of the potential clinical consequences of the variability of drug exposure in daily life. Variations in timing of drug intake are unlikely to result in clinical consequences as long as they do not exceed the forgiveness of a drug. However, the consequences of prolonged dosing intervals are often not exactly known. Package inserts are generally lacking recommendations for the prevention of clinical consequences of deviations in drug execution.

Finally, we introduced adherence monitoring to oral medication as an independent variable in a proposal for a study to compare effectiveness with oral vs. intramuscular vitamin B_{12}. Analogous to *in vitro* platelet aggregation, lipid profiles and blood pressure in the foregoing studies with antiplatelet drugs, lipid lowering drugs and antihypertensives, vitamin B_{12} associated biomarkers should be used as outcome measures of the execution of the oral vitamin B_{12} substitution.

In summary, the aim of this thesis was to develop a new approach for the investigation of drug resistance, where adherence with oral drugs and actual exposure to DDIs should be considered as outcome predictors. For the prospective studies that were designed during this thesis, we combined the polymedication electronic monitoring system (POEMS) with biomarker assessments. First, this new approach allowed setting up a study to investigate intake characteristics of cardiovascular risk patients and possible associations with intermediate outcomes in lipid lowering therapy. Secondly, antiplatelet resistance with aspirin and clopidogrel could be studied with the precise assessment of adherence. Third, this approach served to develop the proposal for a study on the effectiveness of oral vs. intramuscular vitamin B_{12} supplementation in primary care.

1.6. OVERVIEW OF PROJECTS

A. Prevalence of Unreached Biomarker Targets

The effects of treatment with lipid lowering drugs on LDL-C levels and antihypertensive drugs on blood pressure can easily be monitored. For both biomarkers, well established therapeutic target levels exist. In a population-based cross sectional study, the percentage of patients not reaching their respective target levels was quantified, which may serve for estimating the incidence of drug resistance.

- *Walter, P., Messerli, M., et al., Prevalence of Unreached Biomarker Targets Under Antihypertensive and Lipid Modifying Therapy in Community Pharmacies in Switzerland. Internal work report.*

B. Development of a Study Design to Investigate Antiplatelet Drug Resistance

A designated technology to assess multidrug adherence monitoring and adequate biomarkers to measure the response to treatment are the cornerstones of a clinical study to assess factors to antiplatelet resistance with aspirin and clopidogrel. This design allows to study the impact of non-adherence, exposure to DDI and other clinical (e.g. diabetes mellitus, inflammation) or pharmaco-genetic (e.g. CYP2C19 polymorphisms) contributors.

- *Walter, P., Tsakiris, D.A., et al., Fundamental Progress in Investigating Drug Resistance with Electronic Multidrug Compliance Monitoring (e-MCM). J Patient Comp 2011;**1**(2):42-47.*

C. Exploring Associations between Objectively Measured Adherence and Biomarker Response in Lipid Lowering Therapy

Project C1: Multidrug adherence monitoring allowed to precisely measuring various objective adherence parameters. Objective adherence parameters are likely to be influenced by subjective beliefs about the medication. On the other hand, objectively measured adherence parameters may have an effect on biomarker response. Therapy with lipid lowering drugs can serve as an example, where the clinically predictive biomarker LDL-C may be influenced by regular drug intake. In **project C2**, we report on an exemplary case in which irrational timing adherence was elucidated by multidrug adherence monitoring.

- ***C1:** Walter, P., Arnet, I., et al., Pattern of Timing Adherence Could Guide Recommendations for Personalized Intake Schedules. J Pers Med 2012;**2**(4):267-276.*
- ***C2:** Arnet, I., Walter, P.N., Hersberger, K.E., Polymedication Electronic Monitoring System (POEMS) – A New Technology for Measuring Adherence. Frontiers in Pharmacology 2013;**4**:1-6.*

D. Antiplatelet Drug Resistance in Outpatients With Monitored Adherence

The debate on antiplatelet resistance with aspirin and clopidogrel is controversial. Additional to other clinical, cellular and genetic contributors, non-adherence may well be a part of the difficulty to attain the expected inhibition of in vitro platelet aggregation in outpatients. In a prospective study on antiplatelet resistance that was carried out according to the design elaborated in project B, we measured multidrug adherence and other presumed contributors to analyse their impact on resistance.

- *Walter, P., Tsakiris, D.A., et al., Antiplatelet Resistance n Outpatients with Monitored Adherence. Thromb Haemost (submitted).*

E. Response to Vitamin B_{12} Substitution

Commonly, vitamin B_{12} deficiency is treated with intramuscular injections in Switzerland. This study is designed to confirm the non-inferiority of oral high dose supplementation of vitamin B_{12}. Adherence with the oral substitution and the patients' acceptance of the two routes of administration are additional aims that will be addressed by this study.

- *Walter, P., Jeger, C., et al., Acceptance and Biomarker Response with Oral vs. Intramuscular Supplementation of Vitamin B_{12} in Primary Care. Study proposal.*

2. ADHERENCE AND BIOMARKERS

2.1. PREVALENCE OF UNREACHED BIOMARKER TARGETS UNDER ANTIHYPERTENSIVE AND LIPID MODIFYING THERAPY IN COMMUNITY PHARMACIES IN SWITZERLAND

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Internal work report

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39th ESCP Symposium on clinical pharmacy 2010 in Lyon, France.

Introduction

The use of lipid modifying therapy (LMT) and antihypertensive therapy (AHT) for the modification of cardiovascular risk factors is widespread. Both LMT and AHT are established in primary and secondary prevention of cardiovascular events. LMT offers a 25-30% reduction of the relative cardiovascular risk in most of the large randomised trials [38]. The expected reduction of systolic blood pressure (SBP) varies between the classes of antihypertensive drugs, but is similar for diastolic blood pressure (DBP) [39]. The relative cardiovascular risk reduction with antihypertensives varies considerably between primary prevention and patients with specific risks, but has recently been questioned for primary prevention [40]. However, the effect of LMT and AHT is reflected by reductions in low density lipoprotein cholesterol (LDL-C) and by SBP and DBP. In Switzerland, recommendations for the use of LMT mainly rely on the European Society of Cardiology (ESC) and on the International Arteriosclerosis Society (IAS) guidelines [41]. According to IAS, LDL-C values in LMT should be lowered to 3.4 mmol/l (moderately elevated risk categories) and 2.6 mmol/l (high risk and manifest arteriosclerosis) [41]. Blood pressure targets for antihypertensive therapy are 140/90 mm or 130/85 mm Hg for patients with diabetes mellitus [42]. However, a substantial proportion of the treated patients does not reach these biomarker targets and is thus at risk not to take full advantage of the prescribed therapy [4, 43]. The prevalence of resistant hypertension is unknown, but estimates from clinical trials have enumerated resistance rates to 20-30% [2]. Target attainment failure in LMT and AHT is attributed to various genetic and clinical factors [44, 45]. Non-adherence is presumably a major clinical contributor with reported double-digit non-adherence rates for LMT in both primary and secondary prevention [46]. Community pharmacists are in an excellent position to address factors that are associated with a lack of target achievement, such as non-adherence, unfavourable lifestyle and nutrition, drug drug interactions (DDI), incorrect dosing, and pharmaco-genetic contributors. Pharmacological biomarkers could help to identify patients who can profit from pharmaceutical care interventions. Our aim is to describe the prevalence of patients not on target with AHT and LMT.

Methods

The data for this sub-analysis were obtained from a community pharmacy based screening program for cardiovascular risk factors (Herzcheck® campaign) in Switzerland. The collection of data involved blood chemistry using capillary blood samples, blood pressure (BP), body mass index, and lifestyle factors of participants. Blood chemistry analysis included total cholesterol (TC), HDL-cholesterol (HDL-C), LDL-cholesterol (LDL-C), and triglycerides (TG).

Patients with a prescription for AHT were labelled as "not on target" if their BP was ≥ 140/90 mmHg (SBP/DBP) or ≥ 150 mmHg (isolated SBP), while LDL-C > 3.4 mmol/l was the respective criterion for patients with LMT.

Patients with LMT were further labelled as "optimisable" if LDL-C was ≤ 3.4 mmol/l, but HDL-C was < 1.0 mmol/l, TC/HDLC > 5, and/or TG > 2.5 mmol/l.

Results

From a total of 4380 screened subjects, 863 (19.7%) were selected because they had a prescription for either AHT (n=537, 12.3%; age=67.9±10.3 years; 68.5% women), LMT (n=157, 3.6%; age=64.9±10.1 years; 56.7% women), or both (n=169, 3.9%; 68.6 ±9.9 years; 55.6% females).

Of 706 patients with AHT, 256 (36.3%) were not on target because they violated either the systolic/diastolic (n=165, 23.4%) or the isolated systolic BP (n=91, 12.9%) criterion. LMT was prescribed in 326 patients, of which 84 (25.8%) were not on target, while the management was optimisable in another 85 patients (26.1%).

Male patients with higher age were more likely not to be on target with their AHT, while female patients with younger age were overrepresented in the group of patients that did not reach their target in LMT (see table 1). Patients who were treated both with LMT and AHT were more likely to reach their LDL-C and AHT targets.

Table 1. Patients on target and not on target with their AHT and LMT (=mean difference and 95% CI instead of OR)*

Antihypertensive therapy (AHT), N=706				
	Not on target N=256	On target N=450	OR [95% CI]	p-value
Age	69.8 ± 9.7 y	67.0 ± 10.3 y	-2.8 y [-1.2- -4.3]*	<0.005
Women	151 (59.0%)	311 (69.1%)	1.56 [1.13-2.14]	0.007
Cigarette smoking	15 (5.9%)	30 (6.2%)	0.94 [0.49 -1.79]	0.846
Concomitant use of LMT	49 (20.3%)	120 (25.7%)	1.54 [1.06-2.24]	0.024
Lipid modifying therapy (LMT), N=326				
	Not on target N=84	On target + optimisable N=242	OR [95% CI]	p-value
Age	64.0±11.4 y	67.8±9.6 y	3.72 y [6.2-1.2]*	<0.005
Women	58 (69.0%)	125 (51.7%)	0.48 [0.28-0.81]	0.006
Cigarette smoking	8 (9.5%)	21 (6.4%)	1.11 [0.47-2.61]	0.814
Concomitant use of AHT	34 (40.5%)	135 (55.8%)	1.86 [1.12-3.07]	0.016

Discussion

In approximately one third (36.3%) of the AHT and in one quarter of LMT (25.8%), patients failed to reach the biomarker targets. BP and LDL-C represent established surrogate outcomes of the drugs' effect. A gap between the measured biomarker levels and target values according to the guidelines indicates suboptimal therapy effectiveness. However, in the absence of access to clinical data of the patients, the biomarker targets in this study were defined as cut-offs irrespective whether patients took the drugs for primary or secondary prevention or whether they had diabetes mellitus. A multi-center survey in the United States with 4888 patients with LMT found an overall rate of 38% non-achievers of their respective target LDL-C according to the National Cholesterol Education Program (NCEP) guidelines, but the targets were stratified for the patients cardiovascular risk [47]. In a study performed in a U.S. managed care organization, adherence with AHT and LMT as measured by prescription refill data was found to decline sharply following treatment initiation and reached only 35.8% after 12 months [48]. Concomitant initiation of AHT and LMT was independently associated with better adherence in this U.S. study. Better adherence may thus be the background of the higher likelihood of target achievement that was observed in our study when patients were concomitantly treated with LMT and AHT. Thus, non-adherence is reasonably a plausible major contributor to the large proportion of patients who did not achieve their targets in our study.

Strengths and Limitations

Studying target attainment rates in a pre-existing database of patients with AHT and LMT is a simple approach that allowed involving a relatively large patient sample with limited resources. On the other hand, a retrospective analysis is inherently flawed by limited data quality. We had neither reliable clinical or medication data of the patients, nor were we informed about individual therapeutic targets of the patients. Thus it was not possible to evaluate whether the patients received adequate treatments. The biomarker cut-offs that were used to define target attainment have been set at relatively high levels to increase specificity and thus resulted in conservative estimates on resistance to LMT and AHT. Data on prescribed drugs and adherence would be necessary to distinguish between different factors responsible for the failure to attain biomarker targets. The patient data was collected during a health check campaign without distinct inclusion or exclusion criteria, thus the sampling might have been subject to selection and bias.

Conclusion

This study confirmed that a substantial rate of patients fails to attain the biomarker targets in lipid modifying and antihypertensive therapy. Little is known on the differential impact of presumed contributing factors (e.g. pharmaco-genetics, DDI, non-adherence) on the failure to reach the target levels. Remarkably, concomitant antihypertensive and lipid modifying therapy seems to result in better target attainment, presumably due to better adherence. This observation needs further investigation.

Knowledge of factors that are associated with a lack of target attainment is essential and can put healthcare professionals in an ideal position to plan and perform interventions to help patients to take full advantage of the prescribed therapy. Prospective studies with electronic multidrug adherence monitoring are required to disclose the impact of these presumed factors.

References

See general references section.

2.2. FUNDAMENTAL PROGRESS IN INVESTIGATING DRUG RESISTANCE WITH ELECTRONIC MULTIDRUG COMPLIANCE MONITORING (E-MCM)

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Abstract

Background and Purpose

Current definitions of drug resistance are shaped by the pharmacotherapeutic fields they occurred in. They usually mention various contributing factors and refer either to the clinical or the biomarker level. Particular attention has been attracted by antiplatelet resistance, a phenomenon with clinical, cellular and pharmacogenetical contributors. However, the impact of every single factor to antiplatelet resistance in outpatients under prescribed antiplatelet therapy has not been comprehensively evaluated so far, neither has the temporal pattern of drug intake been studied as a possible contributor.

Methods

We propose generally applicable definitions of drug resistance, therapy failure and a classification of contributing factors to drug resistance. We introduce a study design with the use of blisterpacks in a target population (i.e. patients with a prescription of antiplatelet drugs), filled with the entire oral medication regimen, and equipped with electronic multidrug compliance monitoring (e-MCM) allowing thus to evaluate in a stepwise way the impact of the contributing factors (e.g. potential drug-drug interactions, genetic polymorphism) on biomarker outcome (i.e. in vitro platelet aggregation), with proven intake of the polytherapy.

Discussion and Conclusion

Drug resistance should be judged with the knowledge of the contributing factors and in the context of a patient's polytherapy under daily life conditions. The use of electronic multidrug compliance monitoring (e-MCM) allows the ruling out of non-compliance and the evaluation of the impact of potential drug-drug interactions on biomarker outcome. Pharmacogenetic testing may thus be restricted to those patients with a persistent lack of response, and the impact of the genotype may be interpreted within patients' specific clinical context. An evidence-based optimisation of the therapy in case of insufficient biomarker response may thus be given, and the intervention can be stratified according to the identified contributing factors. The debate may then be opened on the clinical benefit and the cost-effectiveness of practices currently used to overcome insufficient effectiveness solely based on biomarker findings.

Keywords: Compliance, drug resistance, electronic multidrug compliance monitoring, pharmacological biomarker.

Background

The term "drug resistance" has emerged from antibiotic and anticancer therapy and has been discussed in many fields of pharmacotherapy, such as antihypertensive drugs [2], antiepileptics [3, 49], antidepressants [50], lipid modifying therapy [4] and antiplatelet medication [51-53].

"Drug resistance" was introduced as a Medical Subject Heading (MeSH) in 1972 and refers to a "diminished or failed response of an organism, disease or tissue to the intended effectiveness of a chemical or drug". This circumscription provides a short and global definition of the phenomenon, but does not specify the clinical context under which resistance is observed. Furthermore, the definition omits to mention if the effectiveness is measured on a clinical level (e.g. mortality) or on the surrogate marker level.

The term "drug resistance" has further been shaped by various authors in the context of their specific field of interest. The different proposed definitions have some basic features in common, like the clinical relevance of drug resistance, its multifactorial aspect, and its detection through pharmacological biomarkers [2-4, 49-53], but no generally accepted concept of drug resistance has emerged.

Antiplatelet Drug Therapy for the Investigation of Drug Resistance

Dual antiplatelet therapy with aspirin and clopidogrel is a well-established regimen in the prevention of stent thrombosis [54], whereas aspirin has proved its efficacy in the primary and secondary prevention of cardiovascular and cerebrovascular events [6]. Up to 20% of patients experience recurrent cardiovascular events despite dual antiplatelet therapy after percutaneous coronary intervention [55]. These incidence rates have raised the question of antiplatelet drug resistance, which is characterised by persistent in vitro platelet aggregation.

The term "antiplatelet resistance" describes "a phenomenon of measureable, persistent platelet activation that occurs in patients with prescribed therapeutic doses of aspirin" [56]. This definition is restricted to a biochemical phenomenon and includes any factor liable to compromise the biomarker outcome, including clinical factors that reduce drug exposure like non-compliance or poor absorption.

Clopidogrel resistance received special attention and was differently named "nonresponsiveness" [57] or "variability in platelet response" [58]. The phenomenon has been associated with CYP2C19 loss-of-function genotype [59] and with drug-drug interactions affecting CYP2C19 and CYP3A4 metabolic capacity [60-62]. Further factors with

possible influence on platelet activity were described, like tobacco smoking [63], diabetes mellitus [64] and systemic inflammation with increased platelet turnover [65]. None of these factors emerged as the most likely cause for the unmet clinical outcome, but their effects on in vitro platelet aggregation are evident.

Non-compliance must be generally suspected when patients under antiplatelet therapy do not display the expected in vitro platelet inhibition. Non-compliance has been described as a contributor of outstanding impact in aspirin therapy [66], with a prevalence of 22% in a cohort with manifest coronary artery disease and stroke [67]. However, when aggregation is inhibited, this means that an appropriate amount of the prescribed drug has been taken to produce the pharmacological effect, not that the prescribed regimen has been adhered to [68]. The contribution of non-compliant behaviour to antiplatelet resistance in outpatients under prescribed antiplatelet therapy has not been evaluated so far.

Definition of and Contributing Factors to Drug Resistance

"The absence of the expected biomarker response under (adequately) prescribed therapy (in correctly diagnosed patients)" may represent the cornerstone of a general definition of drug resistance. Consequently, we support that an unfavourable clinical outcome should be addressed as "treatment failure" [5] while "drug resistance" should be reserved for therapies whose efficacy can be evaluated with pharmacological biomarkers.

When a patient fails to respond adequately to a prescribed treatment, either on a clinical or on a biomarker level, the physician must distinguish among different causes of variability (pharmacological, behavioural, biological). Often, a combination of factors has produced the suboptimal results. Given the above definition of drug resistance, the contributing factors can be classified into clinical, genetic and cellular factors (Table 1), as already proposed for antiplatelet resistance [69]. Each single factor may negatively influence the biomarker response, and the ensuing impact depends on the taken drug.

Table 1. Contributing factors to drug resistance, with specific examples for antiplatelet drug resistance

Factors contributing to drug resistance	**Factors contributing to antiplatelet drug resistance** (aspirin and/or clopidogrel) [5, 69]
Clinical factors	
Prescription	Failure to prescribe; Underdosing
Patient non-compliance	Mostly delayed or omitted doses
Poor absorbance	
Drug-drug interactions	Interaction with ibuprofene (aspirin); Interaction with PPIs and statins (clopidogrel)
Lifestyle factors	Tobacco smoking; Elevated body mass index
Comorbidity	Diabetes mellitus; Acute coronary syndrome; Systemic inflammation
Genetic factors	
Pharmacokinetic	Polymorphisms of MDR1 and CYP isoforms
Pharmacodynamic	Polymorphisms of P_2Y_{12} and GPIIb/IIIa
Cellular factors	
Cell turnover	Increased platelet turnover
Adaptive cellular mechanisms	Increased ADP exposure
Up-/down-regulation of cell metabolism	Up-regulation of ADP-mediated pathways

In summary, we promote the comprehensive assessment of drug resistance with the evaluation of all contributing factors. To this purpose, we propose a study design with the implementation of a new compliance monitoring technology, using the field of antiplatelet resistance as a model.

Aims of the Study

The aims of the study of which the design is presented in this article are to identify resistance to antiplatelet therapy in outpatients with a prescription of antiplatelet agents, and to assess all factors that compromise the biomarker response, i.e. the platelet aggregation.

Methods

Blisterpack and Compliance Measurement Technology

We chose a commercially available weekly blisterpack with 7x4 compartments (Pharmis GmbH, Beinwil a.S., Switzerland), filled with the entire oral medication regimen of the patient (Rx and OTC drugs). The back of the blisterpack is covered with a clear, self-adhering polymer foil (provided by ECCT B.V. Eindhoven, NL) with loops of conductive wires and connected to electronic components (Fig. 1). The attached microchip measures the electrical

resistance, and records the time of its changes when a loop is broken, i.e. when a cavity is emptied. The data is transferred with a wireless communication device (near field communication) to a web-based database.

Figure 1. Electronic multidrug compliance monitoring (e-MCM) system

This electronic multidrug compliance monitoring (e-MCM) system enables the monitoring of the entire pharmacotherapy, and thus assessment of compliance behaviour and drug-drug interactions.

Recruitment and Inclusion Criteria

Patients are recruited at their local general practitioners (GP) surgeries during a routine consultation. Inclusion criteria are the prescription for aspirin and/or clopidogrel for the prevention of primary or secondary atherothrombotic events (cardiovascular, stent thrombosis or cerebrovascular event), or for the treatment of peripheral arterial occlusive disease (PAOD), and the patient's agreement to get a weekly blisterpack with electronics (e-MCM) prefilled with all orally administered drugs and to leave all extra drugs at the study centre. Exclusion criteria are acute cardiac symptoms, residence in a care home or receiving home care, and lack of discernment to manage one's own pharmacotherapy. The use of a pill organiser is not an exclusion criterion.

Biomarkers for Antiplatelet Therapy

Historically, platelet aggregation in platelet-rich plasma was the method of choice to assess in vitro platelet activity [8]. In recent years, new assays have become commercially available. Raising evidence supports the introduction of multiple electrode aggregometry (MEA, Dynabyte, Munich, Germany) for the measurement of platelet aggregation and the prediction of the clinical outcome [20]. In the described study design, MEA is applied to measure in vitro platelet aggregation. The MEA instrument allows two ways to express the AUC: as arbitrary aggregation units (AU • min) or as units (U), whereas 10 AU • min correspond to 1 U. The cut-off value was set at 54 U [70].

Study Plan and Stepwise Assessment of Contributing Factors

At visit 1, demographic data including smoking status, educational level and social background is collected; baseline laboratory data including platelet aggregation is measured, and the individualised blisterpack for one week is delivered. Patients are informed that their drug intake will be electronically monitored, and advised to take their drugs as they were instructed in usual care. Patients' extra drugs are stored at the study centre during participation, thus rendering parallel drug consumption impossible.

At visit 2, one week later, in vitro platelet aggregation is measured and serves to dichotomise the study cohort into subjects with a) sufficient and b) insufficient platelet inhibition. The latter group will get another week of compliance-monitored therapy, with an additional direct observation (DOT, directly observed therapy) of the doses containing the antiplatelet drug on five of seven days.

The assessment of drug-drug interactions and pharmacogenetic polymorphisms is performed in all patients.

Sample Size Estimation

The incidence of antiplatelet resistance in patients with a prescription for aspirin and/or clopidogrel varies widely (8 - 45%) [56]. For circumstances as defined in our study, an incidence of 20-30% seems reasonable. The presence of main contributing factors in the general population is assumed to be 15% for the loss-of-function genotype (g), 60% for drug-drug interactions (d), and 20% for comorbidities (c). Thus, the codes of the different patient groups and the rates of non-responders would be g0d0c0 (2%), g0d0c1 (60%), g0d1c0 (15%), g0d1c1 (65%), g1d0c0 (55%), g1d0c1 (75%), g1d1c0 (75%), g1d1c1 (90%), with 1 if the factor is present, and 0 if the factor is absent. The primary analysis should

demonstrate that the main contributing factors have the expected influence on non-response. A Monte Carlo simulation with adjusted sampling for the estimated overall incidence of non-response resulted in a required total of 493 evaluable patients to achieve a power of 80% as for the primary analysis.

Expected Results

Baseline platelet aggregation at visit 1 mirrors the effectiveness of a patient's polytherapy, i.e. drug efficacy under daily life conditions. We expect the values after one week to show an improved platelet inhibition, independently of the baseline value (and very likely because of the Hawthorne effect), and to draw conclusions on the optimal temporal pattern of drug intake on biomarker outcome with antiplatelet drugs.

With proven compliance by means of e-MCM, we will be able to quantify the clinical, genetic and cellular factors other than non-compliance in patients with insufficient platelet inhibition under aspirin and/or clopidogrel. With the tracking of the entire pharmacotherapy, we will be able to evaluate the impact of drug-drug interaction on the biomarker response, and to make recommendations for action when platelet inhibition is insufficient. We expect differences between both groups (aspirin and clopidogrel) in frequency rates, with a greater importance of pharmacogenetic polymorphisms and drug-drug interactions under clopidogrel therapy. Non-compliance is assumed to have a similar impact on in vitro platelet inhibition for both antiplatelet drugs.

Discussion and Conclusion

The use of electronic multidrug compliance monitoring (e-MCM) for the assessment of drug resistance allows us to rule out non-compliance and to evaluate the impact of potential drug-drug interactions on biomarker outcome. Pharmacogenetic testing may be restricted to those patients with a persistent lack of response. An evidence-based optimisation of the therapy in case of insufficient biomarker response is thus given, and the intervention can be stratified according to the identified contributing factors. The efficacy of the intervention can then be estimated with the biomarker outcome. In essence, the switch to another drug can be proposed only in case of proven inefficacy (genetic polymorphism, comorbidity, inevitable interaction). Our stepwise approach to identify and assess drug resistance in individual patients is applicable to many therapeutic settings, like treatment of dyslipidemia, hypertension, osteoporosis, and congestive heart failure.

To our knowledge, prospective compliance monitoring in patients with antiplatelet drug resistance has not been evaluated so far; neither has the applicability of in vitro platelet

monitoring with multiple electrode aggregation (MEA) in a primary care setting. Insufficiently lowered platelet aggregation with MEA is associated with an unfavourable clinical outcome and thus underlines the relevance of the finding. Stratified interventions may optimise safety and effectiveness of drug therapies under daily life conditions, and back up the utility of diagnostic strategies addressing drug resistance. Further studies are needed to evaluate the clinical benefit and cost-effectiveness of identifying and treating drug resistance in different population groups.

Summary Points

- We support a new definition of drug resistance and propose its attribution to an inadequate biomarker response to prescribed drugs.
- Drug resistance is a phenomenon with multiple contributing factors on the clinical, genetic and cellular level.
- Antiplatelet drug resistance can serve as a model for drug resistance.
- The assessment of contributing factors must involve electronic multidrug compliance monitoring (e-MCM) to rule out non-compliance and to measure exposure to drug-drug interactions.
- More studies are needed to evaluate the clinical benefit and cost-effectiveness of identifying and treating drug resistance in different population groups.

Conflicts of Interest

None declared.

References

See general references section.

2.3. PATTERN OF TIMING ADHERENCE COULD GUIDE RECOMMENDATIONS FOR PERSONALIZED INTAKE SCHEDULES

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Abstract

Deviations in execution from the prescribed drug intake schedules (timing non adherence) are frequent and may pose a substantial risk for therapeutic failure. Simple methods to monitor timing adherence with multiple drugs are missing. A new technology, i.e., the polymedication electronic monitoring system (POEMS) attached to a multidrug punch card, was used in a clinical trial on outpatients with prescribed medicines for vascular risk reduction. The complete delineation of timing adherence allows for the calculation of objective adherence parameters and the linking of exposure with drug-drug interactions. A sub-analysis was performed on 68 patients, who were prescribed lipid lowering therapy. A smaller intake time variability of the lipid lowering drug was significantly associated with better levels of LDL-cholesterol, independently of the time of day. This finding may challenge current general recommendations for the timing of lipid lowering drugs' intake and substantiate that inter-individual differences in timing adherence may contribute to response variability. Thus, objective parameters based on multidrug adherence monitoring should be considered as independent variables in personalized medicine. In clinical practice, personalized intake recommendations according to patients' pattern of timing adherence may help to optimize the effectiveness of lipid lowering agents.

Keywords: Compliance, adherence, time variability, electronic polymedication monitoring, lipid lowering agents

1. Introduction

Patient non-adherence and shortcomings in timing adherence with prescribed drug regimen poses a substantial risk for therapeutic failure, regardless of the disease or patient characteristics [71].

Non-adherence is the result of multiple factors that have been classified into five dimensions [72]. Therapy-related factors, such as co-medication, dosing frequency and intake schedules, are likely to affect the execution of the patients' therapy plans. Numerous direct and indirect methods for adherence measurement have been described [73]. More than 20 years of research on electronic adherence monitoring revealed several patterns of adherence, however focusing only on single drugs [33, 74]. Electronic adherence monitoring proved to be the most sensitive method for adherence assessment and provided the best predictor of health outcomes [75, 76]. The recently introduced polymedication electronic adherence monitoring system (POEMS) allows for monitoring of the intake of all oral solid drugs [77]. The complete delineation of timing adherence with any of the prescribed oral solid drugs allows for assessing whether specific adherence parameters are associated with biomarker outcomes, which are predictive of effectiveness and toxicity. Taking non-adherence is often arbitrarily defined as 80% of doses taken, regardless of the drug, although the rationale for drug-specific and more sophisticated cut-offs could be deducted from pharmacokinetic and pharmacodynamic characteristics [28]. Continuous variables for timing adherence can be helpful to overcome this imprecision. Time variability of drug intake (t_{VAR}) was introduced to describe intra-individual intake variation [25]. Except for oral contraceptives, little is known about the impacts of intake time deviation on drug effectiveness, and no advice can be retrieved from drug labels on what should be undertaken if time deviations or missed doses occur. Pharmacodynamic biomarkers as intermediate outcomes can help to study the tolerability of time deviations in the execution of the drug regimen [78]. Low density lipoprotein cholesterol (LDL-C) is a well-established biomarker that reflects the effectiveness of lipid lowering therapy with statins, and substantial gaps to LDL-C target achievement have been reported [47]. The impact of adherence patterns on LDL-C values was analyzed in the context of a prospective trial on antiplatelet resistance in which adherence was monitored with POEMS [79]. The results presented in this article describe the intake characteristics of an outpatient cohort, their association with the treatment schedule, subjective measures of adherence and biomarker response in lipid lowering therapy.

2. Methods

The parent trial on antiplatelet resistance (ClinicalTrials.gov ID: NCT01039480) was approved by the cantonal ethics committee of Aargau, Switzerland and included patients with a prescription for aspirin and/or clopidogrel, recruited by general practitioners. Patients with a full set of data were included in the analysis, and sub-analysis concerned users of a lipid lowering drug (LLD). Levels of LDL-cholesterol (LDL-C) were used as surrogate outcome for therapeutic effectiveness. All the patients' oral solid drugs were repacked into a multidrug punch card (Pharmis GmbH, Beinwil am See, Switzerland) with 7 × 4 units-of-use for seven days. The backside was covered with a polymer film, which registered the drug removal from each unit-of-use. The POEMS technology consists of 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 patients were advised to take their drugs at the time they were normally used to and to return the punch card upon their second visit after one week. Removal of drugs on demand was recorded, but not considered for analysis. Individual intake schemes were analyzed, regardless of the prescribed treatment schedules. The following parameters were derived from the electronic reports and calculated as follows:

- (a) Time variability of drug intake (t_{VAR}) according to equation (1) [25].

$$t_{VAR} = \frac{\sum_k \left| t_{ik}\text{-median (i)} \right|}{\text{number of prescribed dosing days for subject i}} \quad (1)$$

- (b) Dose-to-dose intervals as the time difference between two consecutive removals.
- (c) Weekend effects as the differences between objective adherence parameters on working days (Monday to Friday) and weekend days (Saturday and Sunday).

Patients' subjective adherence scores were obtained with the Morisky-8 (MMAS-8, score 0 to 8) and the Beliefs about Medicines (BMQ) questionnaires [36, 37]. Subscores for BMQ necessity (score 5 to 25), BMQ concerns (score 5 to 25) and BMQ differential (score −20 to +20) were calculated according to the authors [36]. In brief, higher scores are associated with better adherence.

Blood samples were analyzed with a Coulter® AcTDiff (Beckman Coulter Inc., Brea, CA, USA) for hematology and Cobas® 6000 (Roche Diagnostics Inc., Rotkreuz, Switzerland) for clinical chemistry. Target LDL-C levels were set at 3.4mmol/L and 2.6mmol/L for primary and secondary prevention, respectively. The lipid lowering potency of the prescribed drugs were classified in five groups according to equivalence dose tables in order to control for uneven distribution in the statistical analysis [80].

Statistical Analysis

Values are given as mean ± SD, median, quartiles and percentages where appropriate. Differences between patient groups were analyzed with unpaired t-Tests and the Mann-Whitney U-test, where applicable. Time variables were treated as scaled variables; objective adherence parameters were calculated and compared in a bivariate model using the Spearman rank correlation. A one way ANOVA, followed by *post hoc* LSD test, was used to compare differences of mean intake times between days. Two-tailed p-values ≤ 0.05 were considered significant.

3. Results

3.1. Patient Characteristics

The principal study, conducted between June 2010 and June 2011, was completed by 82 patients. Full sets of data were obtained for 78 patients. The study sample (30.8% women, mean age 66 ± 10 years) consisted of 44 patients (56.4%) with a history of arteriovascular events, and 34 patients (43.6%) were prescribed antiplatelet agents for primary prevention. Patients were prescribed one to 13 (median: five) drugs for oral intake, to take once a day (32 patients, 41.0%), twice (35 patients, 44.9%), thrice (eight patients, 10.3%) or more than thrice daily (three patients, 3.8%) (see Table 1 for more details). Higher dosing frequencies correlated strongly with a higher number of prescribed drugs ($R2 = 0.61$; $p < 0.001$). Antihypertensives were prescribed in 63 patients (82.9%), and 15 patients (19.2%) had an antidiabetic co-medication. Sixty-eight patients (87.2%) received LLD and attained mean LDL-C values of 2.3 ± 0.6 mmol/L (primary prevention; target values <3.4 mmol/L) and 2.5 ± 0.7 mmol/L (secondary prevention; target values <2.6 mmol/L).

Table 1. Therapy plan characteristics for n = 78 patients with full sets of data.

Dosing frequency	Number of drugs		Treatment schedule				N	%
	Median	Range	Morning	Midday	Evening	At night		
1 × daily	3.5	1–7	X				30	38.5
				X			1	1.3
						X	1	1.3
2 × daily	5.0	2–11	X		X		30	38.5
			X	X			2	2.6
			X			X	2	2.6
				X		X	1	1.3
3 × daily	7.0	3–10	X	X	X		5	6.4
			X	X		X	3	3.8
4 × daily	11.0	6–13	X	X	X	X	3	3.8

The median MMAS-8 score was 8.0 (range 4.5–8.0) and indicates a high adherence; the maximum score was reached by 53 patients (67.9%). BMQ subscores revealed a high perception of necessity (median 20; range 6–25) and little concerns (median 8; range 5–20). Patients with secondary prevention had moderately higher MMAS-8 scores (7.7 ± 0.6 vs. 7.3 ± 0.9; p = 0.06) and significantly higher BMQ necessity subscores (20.4 ± 4.0 vs. 17.9 ± 4.2; p = 0.01) than patients with primary prevention. The BMQ concerns score did not differ between these groups.

3.2. Objective Measures of Adherence

The prescriptions of the 78 patients theoretically involved 962 drug removals to be executed during the study participation. All dispensed punch cards were returned at the final visit (100% return rate). Visual inspection performed by the investigator confirmed that all removals were executed, but 47 events were not recorded (4.9% missing data), and 30 events could not be assigned to a drug removal even after a post hoc interview-based verification (3.1% implausible data) due to a deficiency in the recording technology.

See Table 2 for the parameters describing the different intake times. Mean time variability was significantly lower in the morning than in the evening (34:16 min:s vs. 49:31 min:s; p = 0.05).

Table 2. *Description of median intake time and time variability (t_{VAR}) over three intake times for 78 patients. Parameters were calculated when at least three (median) or four (t_{VAR}) records per intake time were available.*

	Morning		**Midday**		**Evening**	
	Median [h:min]	t_{VAR} [min:s]	Median [h:min]	t_{VAR} [min:s]	Median [h:min]	t_{VAR} [min:s]
N	73	72	10	10	39	37
Mean	7:33	34:16	12:00	27:24	19:01	49:31
SD	1:00	28:50	00:33	29:37	1:35	50:43
Median	7:41	30:00	12:09	13:45	18:36	37:17
IQR	7:01–8:14	18:17–40:22	11:56–12:11	11:00–27:34	18:05–19:27	19:43–52:51
Range	4:00–9:23	00:43–228:45	10:28–12:35	6:51–103:26	16:02–23:26	02:43–250:34

Of 46 patients with more than one intake daily (Table 1), 38 had schedules that allowed for the calculation of intervals between morning and evening (see Table 3). Additional doses (midday and/or at night) were prescribed in 10 patients.

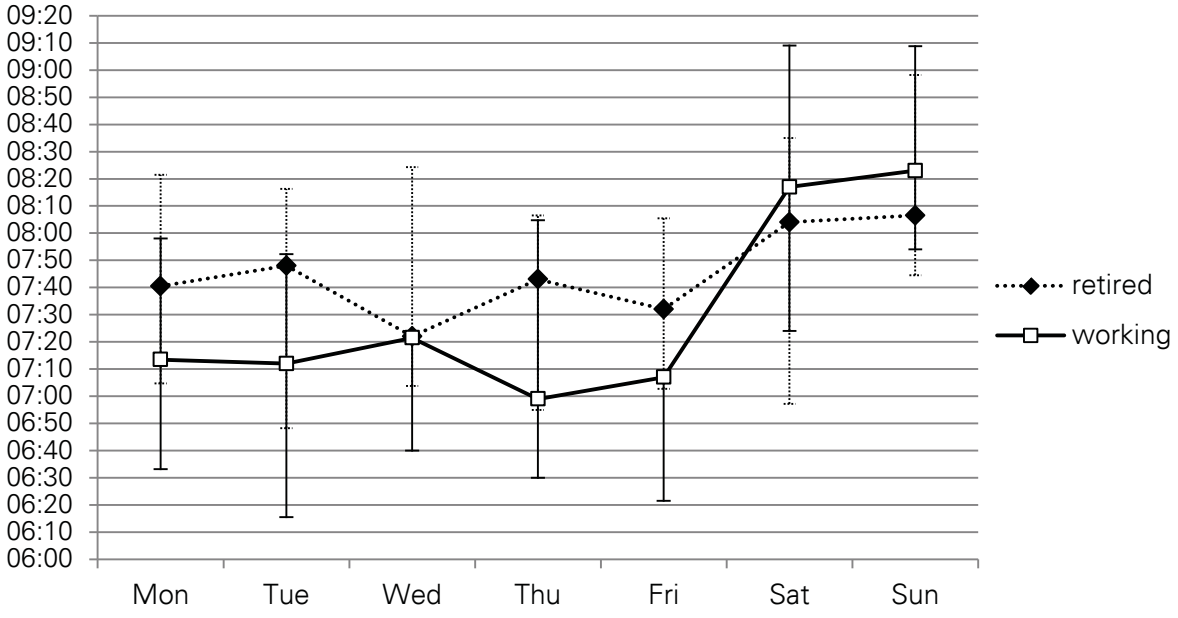
Table 3. Intervals between doses (mean ± SD) for 35 patients with morning-evening schedules (data of three patients were excluded from the calculation due to incomplete pairs).

Treatment schedule	N	Mean interval [h:min]
Morning-Evening	35	11:38 ± 1:49
X-0-**X**-0	25	11:48 ± 1:53
X-X-**X**-0	5	11:33 ± 1:01
X-0-**X**-X	2	10:10 ± 0:52
X-X-**X**-X	3	11:23 ± 3:07
Morning-Midday	8	4:32 ± 1:04
Midday-Evening	7	6:33 ± 0:31

3.3. Weekend-Effect

Mean intake times were significantly delayed on Saturday and Sunday compared to working days ($p < 0.001$). Consequently, the weekend days contributed significantly more to the overall drug intake variation than the working days (23.5 ± 12.7% vs. 10.6 ± 5.1%; $p < 0.001$). This effect was less pronounced in retired patients (N = 41; 30.0 ± 13.5%) than in working patients (N = 30; 18.4 ± 9.8%, $p < 0.001$), but was independently observed in both groups. In absolute numbers, the mean t_{VAR} on working days was comparable in retired and working patients (22:48 ± 13:52 min:s vs. 22:23 ± 22:55 min:s, $p = 0.92$).

Figure 1. Median intake times of the morning doses in retired (N = 41) and working (N = 30) patients. Whiskers indicate the 1st and 3rd quartiles, respectively.



3.4. Socio-Demographic Factors

Time variability over the entire week differed significantly between retired and working patients (25:59 ± 13:44 min:s vs. 45:28 ± 39:28 min:s, p = 0.012) due to the weekend effect mentioned above. A tendency towards higher precision in timing adherence was observed in women compared to men (24:53 ± 13:44 min:s vs. 38:39 ± 33:08 min:s, p = 0.060), while no significant differences were found when patients were grouped by social status, smoking, prevention, treatment schedule (once daily vs. more than once daily) and MMAS-8 scores. Increased age correlated significantly with a more precise timing adherence (Spearman Rho = −0.382, p = 0.001).

3.5. Treatment Scheme and Subjective Adherence

The number of concomitant drugs and the dosing frequency were not associated with time variability of drug intake. Patients' beliefs and concerns, summarized by the BMQ differential score, were in good agreement with subjective adherence reported by the MMAS-8 score (R^2 = 0.376, p = 0.001). This correlation was mainly driven by the BMQ concerns sub-score, which significantly correlated with t_{VAR} (R^2 = 0.242, p = 0.04).

3.6. Biomarker Response

Of the 68 patients with LLD, 22 (32.4%) did not reach their target LDL-C values and had a lower timing precision of the LLD intake compared to the 46 patients (67.6%) who reached their target LDL-C values (t_{VAR} = 67:44 ± 76:22 min:s vs. 28:05 ± 18:54 min:s, p = 0.011). A higher timing variation of the LLD intake correlated with higher LDL-C values (R^2 = 0.323, p = 0.011). In parallel, patients with morning intake of the LLD had a tendency towards lower LDL-C values than patients with evening intake (2.3 ± 0.6mmol/L vs. 2.6 ± 0.7 mmol/L, p = 0.07), but this observation was confounded by a tendency towards higher potency of the LLDs in the morning group (Mann-Whitney U = 5.906, p = 0.05). The t_{VAR} of the LLD intake did not significantly differ between morning and evening LLD intakers (31:29 ± 19:36 min:s vs. 46:29 ± 59:03 min:s, p = 0.2).

4. Discussion

4.1. Main Findings

Biomarker response is an intermediate outcome and can reflect the forgiveness of a drug. In HIV, asthma or blood pressure drugs, electronic adherence was predictive of biomarker outcomes [34, 75, 76]. Safety and effectiveness may be directly linked to the timing adherence to drugs with critical pharmacological properties. For the exemplary case of lipid

lowering therapy, the impact of intake time variability can be estimated from its effects on LDL-cholesterol. LDL-C values typically change within a longer timeframe than in the short period of this study. However, significant time variability may occur, even in a short time frame. In this study, lower LDL-C values were achieved when a precise timing adherence with the LLD was observed, and those patients were more likely to reach their LDL-C targets. Remarkably, this finding was independent of the time of day, although advantages regarding the efficacy of LLD were attributed to the evening intake, at least for those agents with shorter elimination half-lives. Plakogiannis and Cohen found clinical evidence supporting the pharmacologically reasonable evening intake of simvastatin, while data for other statins remained inconclusive [81]. Statins are not known to be markedly sensitive regarding timing adherence. Nevertheless, the results presented here indicate that a regular timing of drug intake may be of more importance than the time of day for the optimization of statins' effectiveness. Given the generally lower time variability in the morning intake times, and in light of the observed association between LDL-C values and the variation in drug intake t_{VAR}, a morning intake of the LLD seems favorable.

However, the limitations to a general recommendation for morning intake become evident when considering the remarkable differences of timing adherence pattern in specific patient groups. Retired patients were more likely to take their morning doses regularly over the entire week, while working patients showed a higher variability of the first daily dose due to a significantly delayed intake on Saturday and Sunday (weekend-effect). A plausible explanation for a lower t_{VAR} in the elderly, e.g. a higher valuation of drug therapy due to disease experiences, was not supported by BMQ scores, which were not age-dependent. Special care should be given to patients with higher concerns, since they showed a higher time variability of drug intake. The results presented here confirm previous reports on the ability of BMQ scores to predict subjective adherence as measured with the MMAS-8 [36].

No further contributors to high t_{VAR} could be identified in the sub-study. The use of a multidrug punch card may have facilitated the achievement of 100% taking adherence, especially for those patients with several intake times per day. Thus, occupational status remains the principal factor influencing electronically measured adherence. Further personalization of drug intake schedules should thus rely on the individual assessment of timing adherence collected by POEMS, unless future studies allow the prediction of timing adherence pattern from the patients' socio-demographic and clinical characteristics.

When studying adherence to lipid lowering (LL) and antihypertensive (AH) drug therapy in a retrospective cohort of 8,506 patients using refill data and the proportion of days covered,

Chapman et al. found the number of other prescriptions concomitant to LL and AH therapy to be the strongest predictor of non-adherence, followed by age, sex and the time between AH and LL therapy initiation [48]. In the presented study, neither the number of drugs nor the number of dosing times per day were associated with differences in objective measures of adherence, leading to the conclusion that the multidrug punch card reduced the complexity of the regimen to an irrelevant factor. Still, age, gender and occupational status remained important determinants of adherence.

4.2. Objectively Measured Adherence and Biomarkers

Balanced intervals between drug intakes are crucial to prevent fluctuations in plasma levels and to avoid the consequences of deprivation and subsequent onset of drug effect. Some authors emphasized the need to consider dosing intervals instead of the percentage of doses taken, which relies on a pharmacologically naive concept [28]. Time variability of drug intake should be interpreted in light of the duration of the action of a drug [25]. In the presented study, monitoring of patient's multiple drug regimen was performed, and this enabled the comparison of timing adherence with the requirements of each drug. Unfortunately, forgiveness has not been characterized for every drug. Except for oral contraception, rationally based procedures to prevent the consequences of drug withdrawal are nonexistent. For drugs whose forgiveness exceeds the timing interval, efficacy should not be affected, but accumulation and toxicity might be more critical [82]. Considerations on time deviations from prescribed schedules have not yet led to regulatory consequences, thus only scarce data exist on time variability of drug therapy and clinical consequences in outpatients.

4.3. Strengths and Limitations

The strength of this study lies in the close monitoring of patient adherence with all oral solid drugs. One of the limitations is the use of unblinded electronic adherence monitoring, which is inherently associated with biased adherence [83]. Further, the limited duration of the monitored period and an artificial and highly adherence-enhancing short term setting may explain the extraordinary 100% adherence rate. Finally, the small sample size limits the impact and generalization of the results. However, data collected with similar methods are scarce and limit the possibility to put the presented findings in the context of previous research.

5. Conclusion

Collecting data on multidrug adherence with POEMS allowed the complete delineation of the patients' pattern of timing adherence with all oral solid drugs. Variations in intake precision and in dose-to-dose intervals were measured, and with the proven 100% taking adherence over the observational period, they could be related to biomarker response. Overall, the intake time variability was more precise with morning intakes than with evening intakes, and a weekend effect contributed to a remarkable variability in working patients. In patients with lipid lowering therapy, a lower time variability of the LLD intake was associated with lower LDL-C values, independently of the time of day. Further research is needed to confirm the impact of timing adherence on the effectiveness of LLD. Future application of POEMS may provide data on adherence patterns and substantiate the rationale for personalized intake schedules based on individual adherence reports.

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Conflict of Interest

The authors declare no conflict of interest.

References

See general references section.

2.3.1. SUPPLEMENTARY RESULTS: TECHNICAL PERFORMANCE OF POEMS

The analysis of data from the above study on the pattern of timing adherence and its association to LDL-C target attainment (see section 2.3.) allowed assessing the technical performance of the POEMS in a clinical study.

Methods

The number of expected removals was calculated from the prescribed dosing regimen. Signals of cavities (ghost-events) that did not contain any drug or that were not created during the patients study participation (between hand-out and hand-in) were not included in the data analysis. Technical problems were identified by visual inspection of the punch card and *ad hoc* verification of the data with the study participants. Missing events were counted when the cavities were emptied, but the removal was not electronically recorded. Events were classified as invalid when they were caused by false handling of the device or when multiple signals were registered for several cavities at the same time. Removals of drugs that had to be taken on demand ("bei Bedarf") were counted separately.

Results

The study was completed by 82 patients. All 997 expected removals from regular drug intake had actually been executed by the patients according to visual inspection, and 885 (88.8%) valid removals were registered. The registered removals represented adherence data of 78 patients, because POEMS did not report any data in 4 patients (see table 4). Technical problems caused 82 missed and 19 invalid events, 16 of which were triggered by a nearby removal. Another 11 invalid events were caused by patients who prepared the removal of the drugs several hours before actual intake. Electronic adherence records were complete in 48 (58.5%) patients with a total of 556 drug removals.

Table 4. Rate of registered events per patient (regular drug intake).

Rate of valid events per patient	Patients	Expected events	Missing events	Invalid events	Valid events
0%	4 (4.8%)	35	35	0	0
1-20%	1 (1.2%)	7	6	0	1
21-40%	2 (2.4%)	35	9	14	12
41-60%	3 (3.7%)	28	12	0	16
61-80%	4 (4.8%)	35	5	5	25
81-100%	68 (82.9%)	857	15	11	831
Total	**82 (100%)**	**997**	**82**	**30**	**885**

The registration of another 65 removals of drugs that were taken on demand corresponded to the number of cavities that have been emptied when returning the punch card. Time and date of the removal was not verified with the patient if the removal pattern was plausible.

Discussion and Conclusion

Reliability and robustness of a technical device is critical for the success of a clinical study, especially if it is used for measuring a primary or secondary endpoint. The POEMS technology allowed registering > 80% of the removals in a large majority (82.9%) of the patients. This representative data collection allowed analysing summary statistics of timing adherence, and the missing data did not corrupt the study results and interpretation. However, quality improvements are necessary to further minimize the rate of missed recordings, e.g. by programming electronic checks of battery charge and blister connection when initializing the device.

2.4. POLYMEDICATION ELECTRONIC MONITORING SYSTEM (POEMS) – A NEW TECHNOLOGY FOR MEASURING ADHERENCE

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Abstract

Introduction: Reliable and precise measurement of patient adherence to medications is feasible by incorporating a microcircuitry into pharmaceutical packages of various designs, such that the manoeuvres needed to remove a dose of drug are detected, time-stamped, and stored. The principle is called "electronic medication event monitoring" but is currently limited to the monitoring of a single drug therapy. Aim: Our aims were introducing a new technology; a clear, self-adhesive polymer film, with printed loops of conductive wires that can be affixed to multidrug punch cards for the electronic adherence monitoring of multiple medication regimens (POEMS), and illustrating potential benefits for patient care. We present a preliminary report with one patient experience. Materials and methods: Our illustrative case was supplied with a prefilled 7-day multiple medication punch card with unit-of-use doses for specific times of the day (6 pills in the morning cavity, 2 pills in the evening cavity and 1 pill in case of insomnia in the bedtime cavity), with the new electronic film affixed on it. Results: The intake times over 1 week were extremely skewed (median intake hours at 2:00 pm for the morning doses and at 6:40 pm for the evening doses). After an intervention aimed at optimising the timing adherence, the morning and evening intake hours became more balanced, with 42.3% of correct dosing intervals (± 3h) for drugs with twice daily intake (vs. 0% before the intervention). Discussion: The electronic monitoring of the entire therapy revealed an intake pattern that would have remained undiscovered with any other device and allowed a personalized intervention to correct an inadequate medication intake behavior. POEMS may guide health professionals when they need to optimise a pharmacotherapy because of suspected insufficient adherence. Further, knowing the intake pattern of the entire pharmacotherapy can elucidate unreached clinical outcome, drug-drug interactions, and drug resistance. In the near future, one could imagine that medication adherence data over the entire therapy plan would be available as soon as the electronic wires are activated, so that a failure to take medication could be detected immediately and intervention could be taken if appropriate.

Keywords: Compliance, adherence, electronic monitoring, multidrug punch card, printed electronics, community pharmacy

1. Introduction

The ideal measurement of adherence has long since been described [68, 84] and should be non-invasive, unobtrusive (to avoid that the drug-taking behaviour of the patient is influenced by the device), objective (to generate reproducible data for each subject), reliable (to insure that the prescribed dose was really taken at the time of package opening), practical and

cheap (to maximize use and minimize costs). It should also yield immediate results and not be open to manipulation. Based on these stringent requirements, traditional, indirect measures (i.e. which do not demonstrate drug ingestion, such as self-reporting, medication diaries, residual pill counting, pharmacy records, clinician opinion) do satisfy many criteria [85]. However, they assume rather than prove the patient's actual drug intake, albeit that they cover longer periods of time. On the contrary, direct methods (i.e. detection of the drug or a metabolic product in a biologic fluid) prove that a dose of a drug was taken but cover brief medication periods. With the emergence of microprocessor technologies in the 1990s, the precise timing of medication-taking behaviour with oral solid forms became feasible, and revealed a comprehensive picture of an individual's day-to-day drug intake that neither drug serum concentrations nor pill counts would have identified. Although electronic compliance-monitoring devices (ECMD) are considered to provide the most accurate and valuable data [86] and are close to a "gold standard" in measuring adherence, they have been mainly used until now as a research tool, owing to their prohibitive cost. Electronic monitoring is used in research areas to measure adherence in population or in clinical studies; to assess determinants of adherence, and to evaluate the effects of intervention on adherence. On the patient level, electronic monitoring allows to calculate dosing intervals, taking and timing adherence; to identify specific patterns of medication use including week-end effects, drug holidays (discontinuing medication use for 24-72h), toothbrush effect or white-coat adherence (increasing adherence several days prior to a medical appointment) and dumping (intentionally discarding medication); to identify days of under- and over-consumption; to link the timing of doses with the efficacy of the drug and with critical health incident [87] to distinguish between probable and improbable drug reactions or side effects [87, 88], and finally to give patients insight into their own dosing history. The ECMD use a microprocessor embedded in a pill bottle cap or in a storage container [89] that records the precise date and time, every instance that the device is opened and closed. The major drawback of the bottle is that it monitors only one lead drug and thus requires one cap per medication, while the container holds up to one month-supply of different pills in its five inner compartments. Due to this setting, data are missing on what was done at each opening; was it to take one or more pills, to remove daily pocket doses or to fill a weekly organizer? [90]. Further, both devices do not accommodate the use of pillboxes [91].

The new technology is composed of printed electronics made of a clear, self-adhesive polymer film with loops of conductive wires that can be affixed to blister packagings. The smart components measure the electrical resistance and record the time of its changes when a loop is broken, i.e. when a cavity is emptied. The data are transferred via a wireless

communication device to a web-based database. This new technology was first developed to fit commercially available standard blister packs [92], avoiding the transfer of pills into an ECMD and keeping the primary packaging. We developed further the electronic film technology to fit on the rear side of a disposable multidose punch card (Fig. 1).

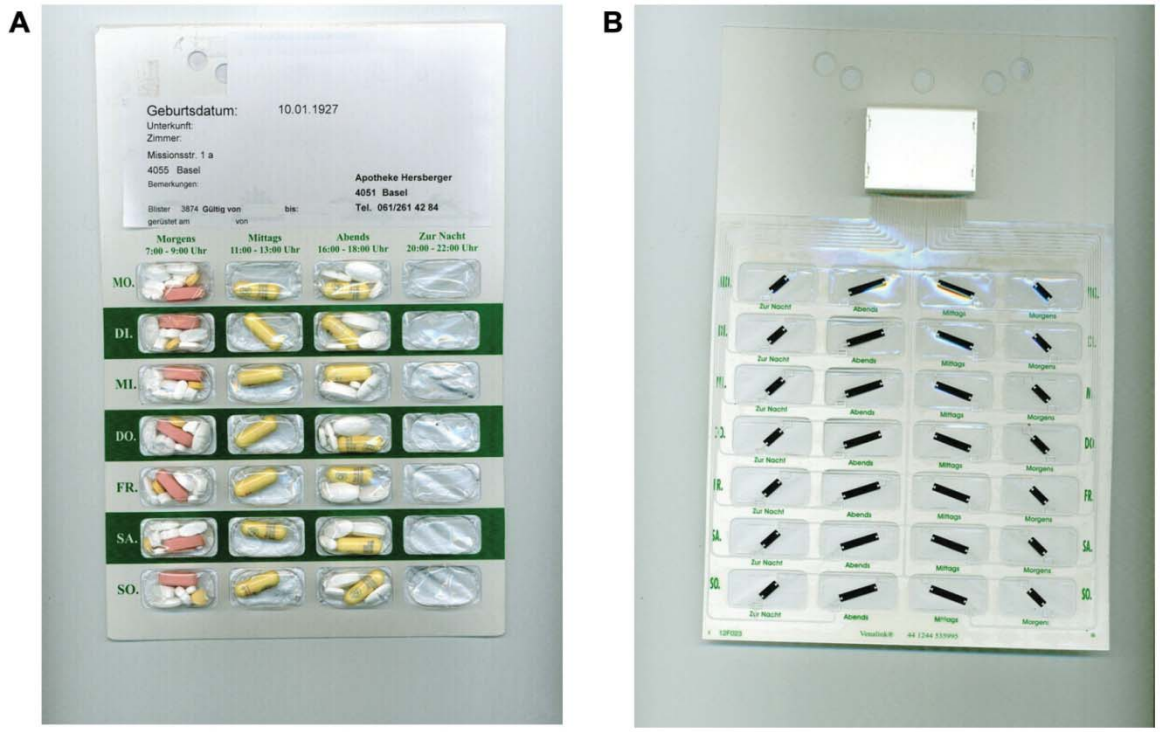


Figure 1. (A) Front side of a commercially available multidose punchcard (Pharmis GmbH, Beinwil am See, Switzerland) with 7 x 4 cavities pre-filled with a patient's individualized medication regimen. (B) Rear side covered with an electronic film of conductive tracks, a battery and an antenna, and a microchip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

This "unit-of-use packaging" consists of sealed calendar compartments with several medications to be taken together in fixed combination, thus avoiding patients from having to use multiple medication packs and bottles. Currently, multidose punch cards are filled manually by a host of community pharmacists e.g., in the UK, Switzerland, Germany, France, Canada and Australia. With the electronic film applied to a multidose punch card, an individualised polytherapy can be monitored by means of the so called Polymedication Electronic Monitoring System (POEMS).

The purpose of this paper is to present an illustrative case using a new technology of electronic adherence measurement of multiple medication regimens with oral solid forms, and to estimate the possible implications linked to this novel technology. We present a preliminary report with one patient experience.

2. Materials and Method

2.1. Extended Case Report

Our patient is a single, recently retired, 65-year-old, Caucasian male. He lives independently (and alone) in an apartment in a medium-sized Swiss city and is in possession of a valid driver's licence. He did have a history of alcohol abuse 20 years previously, which he was able to overcome. Epilepsy was diagnosed in 1974 and is currently controlled with levetiracetam 1000mg twice daily. He is prescribed paroxetine 20mg once daily for the treatment of social phobia and relapsing depression. Persisting, slightly asymptomatic anaemia has been repeatedly investigated without conclusive diagnosis. Probationary treatment with a vitamin B complex twice daily since October 2010 led to a partial correction of the anaemia. Rosuvastatin 20mg and low-dose aspirin 100mg were prescribed once daily for secondary prevention after a cardiovascular incident. Hypothyroidism was picked up in March 2011 and is being treated with levothyroxine 0.1mg once daily. Zolpidem 10mg once daily is being taken when required for difficulty sleeping. The patient was briefly hospitalised in May 2010 for breakthrough seizures. His physician was suspecting non adherence with antiepileptic drugs, while his pharmacist suspected an overconsumption of sleeping pills because the patient would regularly come between the regular refill times, requiring additional zolpidem tablets. Since hospital discharge, the patient was using a pill organizer, refilled weekly by his community pharmacist.

The patient was offered by his physician in August 2010 to get his medication intake monitored, and he accepted. The pharmacist repackaged the entire regimen in a weekly 7x4-cavities punch card with POEMS, with six pills in the morning cavity (levothyroxine, rosuvastatin, aspirin, paroxetine, vitamin B complex, levetiracetam), two pills in the evening cavity (vitamin B complex, levetiracetam) and one pill for sleep disorder in the bedtime cavity (zolpidem). The noon cavity was left emptied. The remainder of the patient's monthly medication was stored at the study centre to ensure that no other medication would be taken beside that prescribed and individually blistered. The patient was informed of the electronic monitoring system and was advised to take his drugs as instructed by his physician.

The following parameters were derived from the electronic reports, where "dose" is defined as "unit-of-use drugs" included in one cavity, according to the therapy plan.

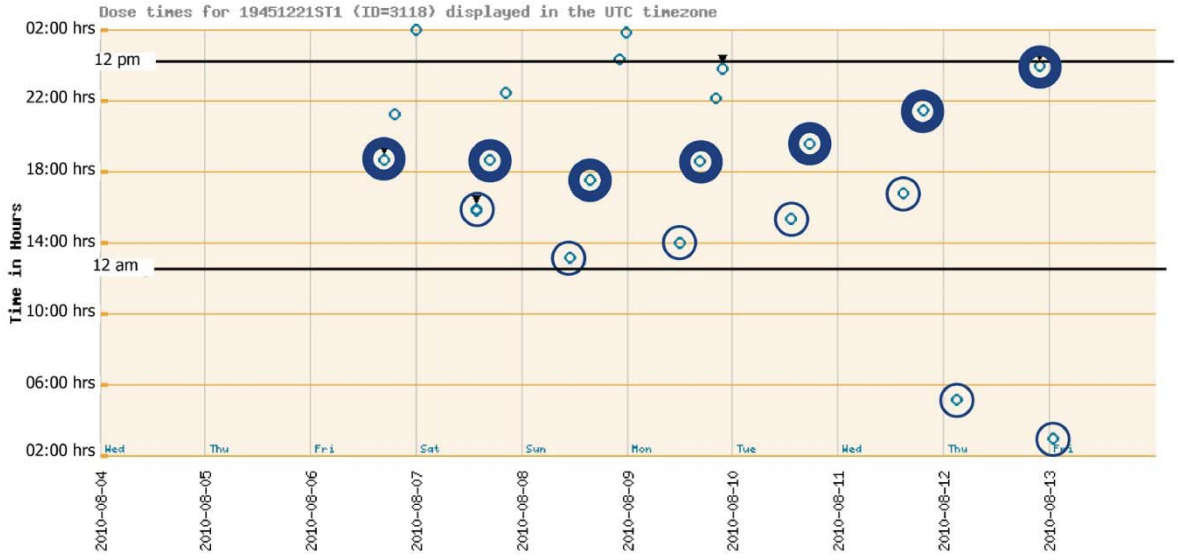
a) percentage overall taking adherence (total doses taken divided by total number of prescribed doses) calculated over the duration of the observational period;

b) percentage of correct dosing days (days taking prescribed dose divided by total days of prescribed dose) calculated over the duration of the observational period;

c) percentage of correct dosing intervals (number of correct dosing intervals divided by total number of prescribed dosing intervals) calculated over the duration of the observational period; a dosing interval is defined as correct if the time between doses is within 25% of the prescribed dosing interval (± 6h for a 24-hour period and ± 3h for a 12-hour period).

3. Results

Laboratory data at baseline showed no abnormalities beside a mild normochromic and normocytic anaemia (haemoglobin 132 g/l [norm 140-180 g/l]; red blood cells 4.35 T/l [norm 4.5-5.5 T/l]). The very low cholesterol level (2.9 mmol/l [norm <5.0 mmol/l]) suggested that the patient was taking his lipid lowering agent well. The first weekly report of the monitored pill intake is given in Figure 2.



Aug.	Fri 6	Sat 7	Sun 8	Mon 9	Tue 10	Wed 11	Thu 12	Fri 13
	O 18:40 ✶ 21:13	✶ 01:58 O 15:48 O 18:40 ✶ 22:27	O 13:08 O 17:31	✶ 00:18 ✶ 01:47 O 14:00 O 18:36 ✶ 22:09 ✶ 23:47	O 15:17 O 19:33	O 16:47 O 21:25	O 05:06 O 23:54	O 02:55

Figure 2. Adherence report over 1 week after inclusion (August 2010). The electronic punchcard was handed out on Friday morning, with the first cavity to be opened on the Friday evening. The spots (see graph) reflect a pushing through of all drugs contained in one distinct cavity as recorded with date and time (see table) by the electronic wires in the film. Morning and evening doses are highlighted. Bedtime doses could be taken when needed. Key: ◎ ○ Morning doses ◎ O Evening doses ○ ✶ Bedtime doses

The patient started his daily activities around noon. Median intake hours, mean intervals between doses and adherence parameters are given in Table 1. As intervals between morning and evening doses were skewed compared to the theoretical 12-hour dose interval for a twice daily intake, the percentage of correct dosing intervals for drugs contained in morning and evening doses, such as levetiracetam (intake ± 3h every 12h) was 0%. The opening times of the bedtime cavities containing the sleeping pills showed a doubling of the dose during the first days of the week, leaving the patient without sleeping pills for the rest of the week.

Table 1. Intake times, intervals between doses and adherence parameters for the two periods of adherence monitoring before (August 2010) and after (December 2010) the individualised intervention.

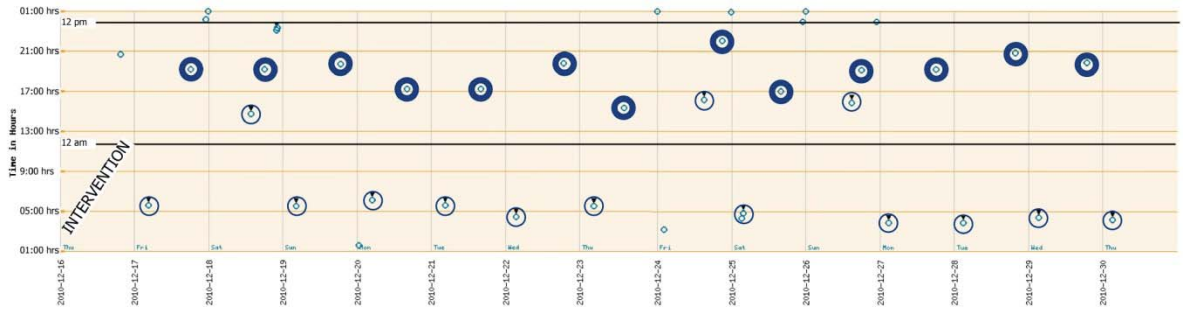
	Before intervention *(7 days in August 2010)*	*After intervention* *(14 days in December 2010)*
Time of intake in the morning 8 am [median] (interquartile range)	2:00 pm (10h 42min)	5:29 am (6h 08min)
Time of intake in the evening 8 pm [median] (interquartile range)	6:40 pm (2h 49min)	7:09 pm (2h 38min)
Intervals between morning doses [mean ± SD]	21h 51min ± 5h	23h 53 min ± 7h 31min
Intervals between evening doses [mean ± SD]	24h 50min ± 1h 15min	24h 03min ± 3h 10min
Intervals between morning and evening doses [mean±SD]	6h 57min ± 6h 34min	11h 28min ± 4h 28min
Intervals between evening and morning doses [mean±SD]	16h 07min ± 7h 28min	12h 25min ± 5h 59min
Overall taking compliance	100%	102.5%
Correct dosing days*	100%	100%
Correct dosing intervals morning e.g. Acetylsalicylic acid (24h±6h)	83.3%	53.8%
Correct dosing intervals morning and evening e.g. Levetiracetam (12h±3h)	0%	42.3%

**without optional bedtime doses*

A measurement-guided medication management (MGMM) programme [86] was implemented by the physician after viewing the records of the polymedication adherence monitoring. Providing patients with feedback of their dosing histories has been shown to positively modify adherence behaviour, either with cue-dose training [93] or by raising awareness of the implications of current behaviour [94]. Thus, an intervention using elements of the ACE-ME model (assessment, collaboration, education, monitoring and evaluation) [95] was planned with the pharmacist. The method of motivational interviewing [96] should be used by the pharmacist, i.e. open-ended questions, reflective listening, affirmation, and summarisation to help the patient express his concerns about the

behavioural change, enhance his personal motivation, set goals and arrive at a change of plan. The planned intervention should focus on the distorted dosing intervals. The objective of the intervention should be the improving of the patient's timing adherence. After the final preparations were made, a session of two hours was scheduled for the intervention and took place at the community pharmacy on Thursday, 16th December 2010. The reports of the intake pattern were printed out and discussed with the patient. The patient was instructed that paroxetine needs to be taken in the morning because of possible activating side effects, such as nervousness or difficulty sleeping, which are undesirable in the evening. A second aspect was the twice daily intake of the immediate release tablets: levetiracetam. The pharmacist explained that intake 12 hours apart would result in constant plasma concentrations, whilst minimising concentration-related adverse effects, such as hostility/aggression, anxiety, insomnia and nervousness/irritability [97][European Medicine Agency (EMA), 2009, last updated 11/2011]. The patient should start on the next day morning with the new intake behavior he agreed on.

The records of the next 14 days subsequent to intervention are shown in Figure 3. A punch card was handed out every Thursday afternoon, with the first cavity to be opened on the Friday morning. The last visit was scheduled for the morning of Thursday, December 30th. Overall taking adherence after intervention was 102.5% due to the anticipated consumption of sleeping pills before the last visit (Table 1). Time lapse between the 14 morning doses was close to the theoretical 24 hours. The morning-evening and evening-morning intervals were close to 12 hours and showed a higher constancy than before the intervention. As a consequence, the percentage of correct dosing intervals for drugs contained in morning and evening doses, such as levetiracetam (every 12h ± 3h) reached 42.3% compared to 0% before intervention. The physician received the records, discussed them with the patient at the next visit, prescribed a double dose of the sleeping pills and planed another session with the pharmacist aimed at motivating further the patient to persist in keeping his new intake pattern.



Dec.	Fri 17	Sat 18	Sun 19	Mon 20	Tue 21	Wed 22	Thu 23	Fri 24	Sat 25	Sun 26	Mon 27	Tue 28	Wed 29	Thu 30
	○ 05:32 ● 19:10	✶ 00:07 ✶ 00:59 ○ 14:40 ● 19.07 ✶ 23:04 ✶ 23:04 ✶ 23:20	○ 05:28 ● 19:39	✶ 01:34 ○ 06:05 ● 17:11	○ 05:34 ● 17:10	○ 04:26 ● 19:47	○ 05:31 ● 15:19	✶ 00:57 ✶ 03:07 ○ 16:10 ● 22:00	✶ 00:53 ✶ 04:16 ○ 04:47 ● 16:58 ✶ 23:56	✶ 00:56 ○ 15:51 ● 19:06 ✶ 23:53	○ 03:52 ● 19:09	○ 03:52 ● 20:49	○ 04:22 ● 19:50	○ 04:08

Figure 3. Adherence report over 2 weeks after the intervention (December 2010). The y-axis reflects local time after adjusting for winter time (– 1h). A punch card was handed out every Thursday afternoon, with the first cavity to be opened on the Friday morning. Morning and evening doses are highlighted. Bedtime doses could be taken when needed.
Key: ◎ ○ Morning doses ● Evening doses ○ ✶ Bedtime doses

4. Discussion

We present a new and innovative film technology for monitoring adherence to multiple medication by means of a single case of a patient implementing a complex dosing regimen. To the best of our knowledge, this is the first time that drug intake patterns of an entire pharmacotherapy, scheduled at 8am, 8pm and bedtime, have been monitored accurately and objectively in real time. The problems suspected over months by the treating physician and the community pharmacist in the reported case (seizures due to insufficient adherence, overconsumption of sleeping pills) could not be solved satisfactorily with the measures then at disposition, like dispensing the medication in a pillbox. Only the electronic monitoring of the entire pharmacotherapy revealed the irregular pattern of the medication intake and the selective consumption of sleeping pills. The pattern would have remained undiscovered if only one lead drug had been tracked e.g., with an electronic pill cap; and even unsuspected if the tracked drug had to be taken in the evening (mean interval between evening doses: 24h 50min). A personalised and targeted intervention could only be set up after the health professionals were aware of the distorted medication use. Thus, Polymedication Electronic Monitoring System could guide health professionals when they optimise the treatment of patients whose unsatisfactory clinical outcome is suspected to depend on insufficient adherence behavior. This new technology could thus find its place in ambulatory care e.g., in specific patients when physicians suspect any form of deviant adherence, as well as in clinical trials e.g., with critical drugs or expensive drugs, when non adherence must be excluded with strong certainty. The actual costs of the multidose punch cards are low

(around Euro 2.- for one punch card), and the Swiss health insurance reimburse the adherence aid delivered by a community pharmacist as a cognitive service. The electronic film as research prototypes are at a high price, that will decrease as soon as the production can be automated, and reach an affordable price.

One limitation inherent to the electronic monitoring of medication use is that the patient gets no other medication than the individually repackaged drugs, in order to prevent any extra medication intake that would not be recorded. The lack of medication stock as well as the obligation to have punctual refills might be a constraint too strong for some patients and might represent a selection bias in larger studies. However, some patients welcome the simplification obtained with one mutidrug punch card and the suppression of the different primary packagings. Further, some patients may be reluctant to use this technology because they may feel under surveillance. However, when the monitoring is not presented as a supervision but as a way to treatment optimisation, one can suppose that the patients will accept an electronic monitoring. We observed also a marked curiosity from our patient as well as a certain desire to compete with the technique.

When searching for a gold standard for adherence monitoring, electronic films affixed to multiple medication punch cards appear to fill all the criteria, i.e. they are non-invasive, unobtrusive, objective, and user friendly. In addition, the transparent compartments on the front side facilitate visual verification of the pre-filled medication and contribute to the safety of drug intake. The monitoring of a multiple drug regimen depicts the intake times of all drugs and thus, enables to evaluate complex drug-effect relationship like drug resistance and drug-drug-interactions. Finally, the new system is usable, even when a patient is used to storage devices like a pillbox.

Some studies showed that short message services (SMS) sent automatically to patients at the appropriate time without interference of a healthcare professional have positive effects on adherence rate [98]. Further, first results with transmission of adherence data through telephone connection in real-time showed the feasibility of the immediate monitoring and its potential to give feedback when a dose of a drug is not taken. Thus, in the near future, one could imagine that medication adherence data over the entire therapy plan would be available as soon as the electronic wires are activated, so that a failure to take medication could be detected immediately and intervention could be taken if appropriate, like sending a SMS reminder. We are well aware that we present a single case to depict new emerging fields of monitoring a polymedication. Further studies are needed to confirm the

generalizability of our findings and to establish the place of POEMS in ambulatory care and in clinical trials.

Declaration of Interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. This work was supported by the Pharmaceutical Care Research Group, Basel, Switzerland. There was no external funding for the study.

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References

See general references section.

3. ANTIPLATELET RESISTANCE

3.1. ANTIPLATELET RESISTANCE IN OUTPATIENTS WITH MONITORED ADHERENCE

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Thrombosis and Haemostasis (submitted)

Abstract

Antiplatelet resistance with aspirin and clopidogrel has been associated with clinical, cellular and pharmaco-genetic factors, and non-adherence has been considered as a major contributor to resistance in outpatients. We aimed at assessing factors to resistance when adherence to the antiplatelet drugs and all other oral solid drugs was controlled for. We tested arachidonic acid and/or ADP-induced in vitro platelet aggregation of 82 outpatients with chronic aspirin and/or clopidogrel treatment before and after a one week period of measuring the patient's adherence with the polymedication electronic monitoring system (POEMS). Resistance was found in 20% (aspirin; n=69) and 25% (clopidogrel; n=32) of the patients after monitored adherence. Mean platelet aggregation was not (aspirin) or non-significantly (clopidogrel) lowered when compared to baseline. Diabetes mellitus and inflammation were consistently associated with resistance to both drugs, and CYP2C19 polymorphisms could not be confirmed as predictors of clopidogrel response. Electronically compiled multidrug dosing histories allowed the concomitant intake of high-dose lipophilic statins to be identified as a risk factor and revealed that exposure to further drug-drug interactions (DDIs) was too low for analysis. Multidrug adherence monitoring allowed thus dismissing non-adherence as a major contributor to resistance and analysing the impact of DDIs according to the actual exposure to the interfering drugs. Further studies based on this methodology are essential to prevent misleading results due to incomplete adherence and gain additional insight into the impact of timing adherence on antiplatelet drug response.

Bullet points

What is known on this topic

- Antiplatelet resistance with aspirin and clopidogrel is caused by clinical, cellular and pharmaco-genetic factors and is associated with an increased risk of therapeutic failure.
- Non-adherence was found accountable for antiplatelet resistance in 14% of the aspirin users and 22% of the clopidogrel users in studies where adherence was estimated from retrospectively measured surrogate markers of antiplatelet drug intake.
- Controversial findings on the impact of drug-drug interactions (DDIs) and pharmaco-genetic contributors to antiplatelet resistance are subject of an on-going debate.

What this paper adds

- We present the results of the first study on antiplatelet resistance with prospective electronic monitoring of outpatient adherence with all oral solid drugs, including those potentially involved in DDIs with the antiplatelet drugs.
- Non-adherence was dismissed as a major contributor to antiplatelet resistance, which persisted in 20% of the aspirin users and 25% of the clopidogrel users despite electronic adherence monitoring.
- Masquerade of non-adherence as antiplatelet resistance and statistically diluted effects of DDIs can be limited by electronic monitoring of multidrug adherence.

Background and Introduction

Antiplatelet resistance with clopidogrel and aspirin has become a widely debated phenomenon in the past decade. A consensus on the definition of has not been reached, but antiplatelet drug resistance is commonly understood as the failure of sufficiently inhibiting platelet aggregation in patients with prescribed antiplatelet medication. A lack of standardisation together with the fact that different commercially available assays do not identify the same patients as resistant contributed to the large variation of reported aspirin resistance [99-101]. Furthermore, difficulties persist in defining how much platelet inhibition is sufficient for protecting patients from clinical events. The multifactorial background of antiplatelet resistance is well accepted and involves clinical, cellular and pharmaco-genetic factors [102]. Diabetes mellitus and inflammation have repeatedly been associated with impaired response to antiplatelet agents. The debate about the impact of pharmaco-genetic polymorphisms on clopidogrel response is ongoing [64, 103, 104], and data on the relevance of drug-drug interactions (DDI) with proton pump inhibitors (PPI) and other potentially interacting drugs on clopidogrel resistance have not always been conclusive [60, 105-108]. The DDI between aspirin and ibuprofen is pharmacologically well characterised, but its clinical impact is unclear [109]. Many authors have emphasised the role of non-adherence in antiplatelet resistance with both aspirin and clopidogrel [99, 110-112]. Data on the impact of non-adherence rely on estimates or assumptions from indirect measures such as plasma drug or metabolite levels [66, 67]. To our knowledge, no antiplatelet resistance study with prospective electronic adherence monitoring has thus far been performed. We used a new electronic adherence monitoring system to overcome the observed methodological shortcomings [79]. In the reported study, we aimed at determining the incidence of antiplatelet resistance with aspirin and clopidogrel in outpatients with monitored adherence and at assessing the contributing factors thereof.

Methods

This observational cross-sectional trial was approved by the ethics committee of the canton Aargau and Solothurn, Switzerland, and has been registered at ClinicalTrials.gov ID NCT01039480. The study was conducted in accordance with the Declaration of Helsinki and correspondent to the ICH-GCP guidelines.

Patient Recruiting

Recruitment was initiated in a convenience sample of 19 general practitioners (GPs) in the area of Olten, Switzerland. They approached their patients with on-going prescriptions for

aspirin and/or clopidogrel upon a routine consultation at their surgery regardless of the diagnosis. For patients who agreed to participate, the GPs transmitted a patient record with key demographic and clinical data to the study centre. Within two weeks after reception of the record, the patients were contacted from the study centre by phone and invited for a first visit in the study centre 1 – 2 weeks later. The patients were requested to bring their actual oral solid drugs and, in the meantime, to take their medicines "as usual".

Visits, Questionnaires and Adherence Monitoring

After written informed consent was obtained at the beginning of visit 1 at the study centre, reconciliation was made between actual drugs and prescriptions, and the use of over-the-counter drugs was verified. Any divergences were cleared before all oral solid drugs were repacked into a multidrug punch card for one week. The patients underwent venous blood sampling and filled in a questionnaire on socio-demographical characteristics and clinical data including self-reported height and weight to calculate the body mass index (BMI). Additionally, the Beliefs about Medicines Questionnaire (BMQ) [36] and the 8-item Morisky Medication Adherence Scale (MMAS-8) [37] were filled in by the patients to measure subjective adherence. Patients returned for visit 2 after 7 days, where they brought back the empty punch card and again underwent blood sampling.

The multidrug punch card was equipped with the polymedication electronic monitoring system (POEMS) to collect objective data on the patient's adherence to his entire oral solid medication. POEMS consists of a polymer film with imprinted electronic wires connected to a microchip that records time and date when a cavity is opened. Further details on the POEMS technology and the definition of objective adherence parameters (intake times, intervals, time variability of drug intake t_{VAR}) have been outlined elsewhere [79, 113].

Patients were classified as diabetics if they had a prescription for oral antidiabetics, insulin or both. Laboratory signs of inflammation were defined by a white blood cell count >9 G/l or C-reactive protein >5 mg/l at visit 1.

Pharmacological Biomarkers

Routine clinical chemistry tests were performed on a cobas® 6000 analyser (Roche Diagnostics, Rotkreuz, Switzerland) at visit 1. Blood cell counts on Coulter AcT_{Diff} (Beckman Coulter, Brea, CA, USA) and *in vitro* platelet aggregation measurements with the MULTIPLATE® assay (Dynabyte, Munich, Germany) were performed at visit 1 and visit 2. Pharmaco-genetic analysis in clopidogrel users was done with the CYP2C19+ assay on the INFINITI® analyser (AutoGenomics Inc. Vista, CA, USA). The MULTIPLATE® ASPItest

(aspirin) and the ADPtest (clopidogrel) were used to specifically test platelet aggregation with the respective antiplatelet drug. The TRAPtest was run as a positive control for general platelet aggregability. Blood samples were collected with a 21-gauge needle by direct venepuncture. Whole blood for the MULTIPLATE® tests was drawn into BD Vacutainer® tubes containing 200 U/ml hirudin (Dynabyte, Munich, Germany) after previous collection of a serum sample and gently inverted 6-8 times to allow mixture with the anticoagulant. EDTA-containing tubes for platelet counts were drawn subsequent to the hirudin tubes in order to avoid cross contamination. No further transportation was performed, and the tests were carried out between 60 and 120 minutes after sample collection. The manufacturer's proposed reference values for the MULTIPLATE® ASPItest, ADPtest and TRAPtest were confirmed in a pre-study with 21 untreated healthy volunteers (10 men, 11 women). Accordingly, resistance was defined by aggregation values above the cut off values of 30 arbitrary units (AU) for the ASPItest and 53 AU for the ADPtest.

Differences in platelet aggregation values between visit 1 and visit 2 (ΔASPItest for aspirin users and ΔADPtest for clopidogrel users) were calculated, with high differences being indicative of poor adherence prior to study participation.

Statistical Analysis

The sample size estimation was based on a Monte Carlo simulation with adjusted sampling for the estimated overall incidence of non-response. A total of 493 evaluable patients were required to confirm genetic variability, drug-drug interactions and co-morbidities as contributing factors with a power of 80%. Given the exploratory character of this study with limited resources, we aimed at including 80 patients to confirm feasibility and plausibility of our approach. Normal distribution of the data was tested with the Kolmogorov-Smirnov test. Normally distributed values were reported as mean±SD or 95% confidence intervals (CIs). Statistical comparisons of continuous variables between patient groups were performed with t-test or the Mann-Whitney U test for unpaired samples. Categorical variables were expressed in %, and the X^2-Test was used to detect an uneven distribution between groups, while Fisher's exact test was used when any expected cell count for a 2 by 2 table was < 5%. The frequencies of factors to resistance with aspirin were compared between resistant and non-resistant patients. Spearmans Rho (ρ) was used to express correlations between continuous variables. The impact of factors to resistance with clopidogrel was analysed by comparing the mean platelet aggregation in patients grouped by the respective factor. Statistical significance was set at 5%. Statistical analysis was performed with the SPSS

software (Statistical Package for the Social Sciences, version 20 for PC, SPSS Inc. Chicago, IL, USA).

Results

Patient Characteristics

Between June 2010 and June 2011, 82 patients successfully completed the study and were included for analysis (see figure 1). In patients on a dual antiplatelet regimen (n=23), aspirin was combined with either prasugrel (n=4) or clopidogrel (n=19). Together with the patients with antiplatelet monotherapy, this resulted in two overlapping samples of 69 patients with aspirin and 32 patients with clopidogrel. All aspirin users except for one patient with an immediate release formulation and two patients with 300 mg aspirin were prescribed enteric coated tablets containing 100 mg aspirin. All clopidogrel users were prescribed the standard maintenance dose of 75 mg.

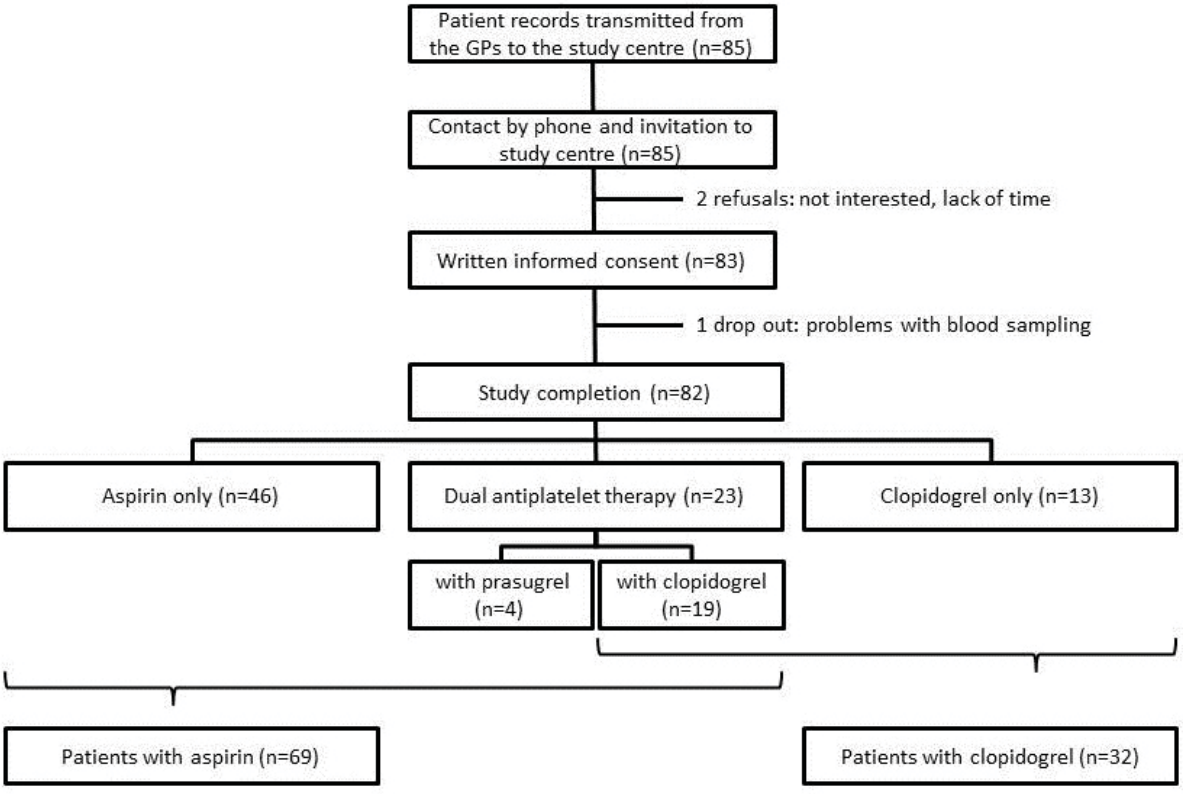

Figure 1. Study flow chart and constitution of the patient samples

The entire patient sample (n=82) consisted of 58 (71%) men and 24 (29%) women with a mean age of 66±10 years and a BMI of 28.1±4.2 kg/m^2. Laboratory signs of inflammation were found in 15 (18.3%) patients. No platelet counts below 100 G/l were observed and the patients' TRAPtest results (visit 1: 112±30 AU; visit 2: 117±27 AU; reference range: 84-128 AU) confirmed good general aggregability. An array of clinical chemistry and hematology

tests showed results within the expectable range of the studied patient sample. The most frequently prescribed concomitant medication consisted of antihypertensives (n=63, 78.8%) and lipid-lowering drugs (n=68, 82.9%), while 15 patients (18.3%) received oral antidiabetics or insulin. Nineteen patients (23.2%) were smokers.

Aggregometry and Resistance

The values of platelet aggregation before and after adherence monitoring are shown in figures 2 and 3. Platelet aggregation values exceeding the respective cut-offs for resistance at visit 2 were observed for 14 (20.3%) aspirin users and 8 (25%) clopidogrel users, resulting in an overall resistance rate of 26%.

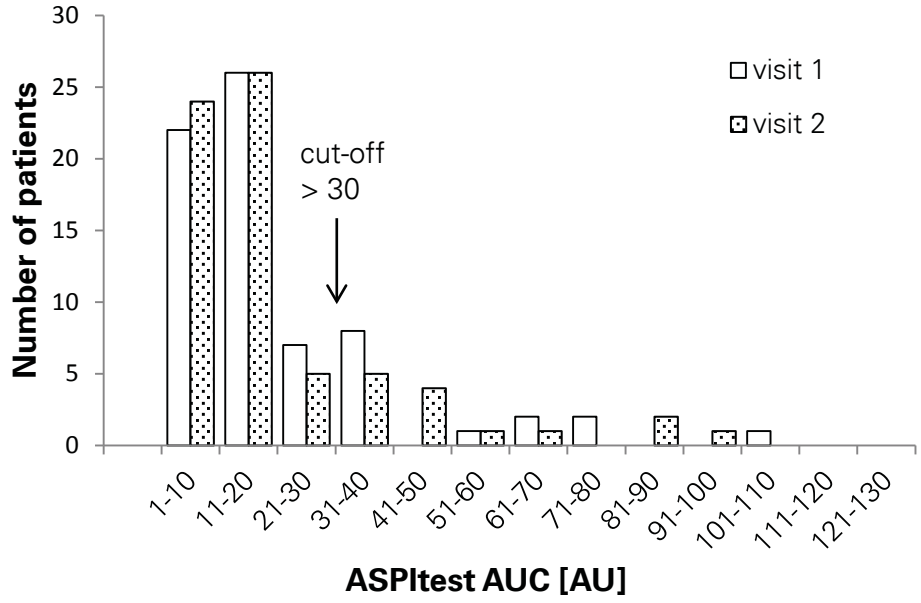

Figure 2. *Distribution of platelet aggregation in 69 aspirin users at visit 1 (before adherence monitoring) and visit 2 (after adherence monitoring). ASPItest values > 30 AU indicate resistance.*

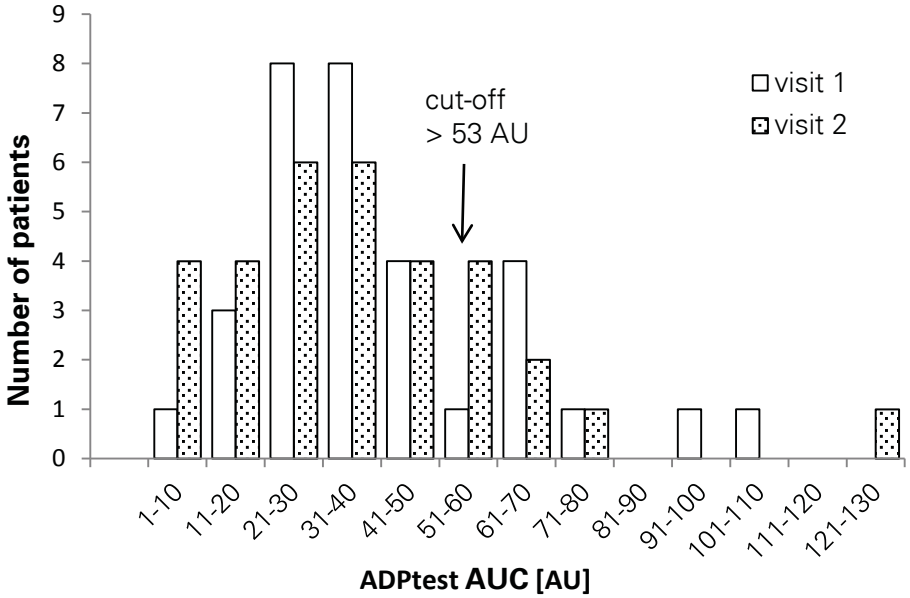

Figure 3. Distribution of platelet aggregation in 32 clopidogrel users at visits 1 (before adherence monitoring) and visit 2 (after adherence monitoring). ADPtest values > 53 AU indicate resistance.

The mean platelet aggregation values before and after adherence monitoring did not differ in the 69 aspirin users (20.3±19.1 vs. 20.3±19.5 AU, p=1.00, paired t-test) and showed a slight tendency towards better aggregation at visit 2 for the 32 clopidogrel users (40.6±22.5 AU vs. 36.8±23.7 AU, p=0.11, paired t-test). The equality (aspirin) and the low difference (clopidogrel) between mean platelet aggregation values at visit 1 and 2 resulted from shifts in both directions, which were mostly small and thus attributable to technical and biological variability. Relevant absolute ASPItest differences > 10 AU between the two visits were observed for 12 aspirin users and resulted in a switch regarding responder status for 4 patients, 2 in each direction.

From 10 clopidogrel users with absolute ADPtest differences > 10 AU between the two visits, 7 shifted towards a better platelet inhibition (of which 3 patients with ΔADPItest < -30 AU), while 3 shifted inversely towards a lower inhibition. This led to a switch of the responder status in 4 patients, again with 2 in each direction.

Of the 19 patients on dual antiplatelet treatment with clopidogrel and aspirin, 4 patients (21%) with isolated clopidogrel resistance and 1 patient (5%) with combined antiplatelet resistance were observed. Isolated resistance with aspirin (when patients responded to clopidogrel) was not observed. All three patients with clopidogrel monotherapy and resistant to the drug had a history of clinical failure with aspirin. They were switched to clopidogrel, but had never been tested for resistance with any of the antiplatelet drugs.

Associated Factors of Resistance

Age and BMI did not differ between resistant patients and responders, neither in aspirin nor in clopidogrel users (see table 1). Inflammation and diabetes mellitus were associated with resistance to both antiplatelet drugs, but statistical significance was limited to aspirin. Additionally, aspirin resistance was significantly more often observed in patients who received aspirin only and who were treated for primary prevention.

Table 1. *Distribution of factors to resistance in aspirin and clopidogrel users (n.a.=not applicable). P-values refer to the results of t=unpaired t-tests, X^2=Pearsons Chi-square test or F=Fisher's exact test.*

	Aspirin			**Clopidogrel**		
Factor	Study sample N=69	Resistant patients N=14	p-value	Study sample N=32	Resistant patients N=8	p-value
Age [years]	65±10	65±10	0.965 (t)	65±11	66±8	0.916 (t)
Women	16 (23%)	4 (29%)	0.642 (F)	7 (22%)	0 (0%)	0.103 (F)
BMI [kg/m^2]	27.8±3.6	30.0±5.8	0.208 (t)	27.6±3.6	27.9±6.9	0.892 (t)
Diabetes mellitus	13 (19%)	7 (50%)	0.002 (F)	6 (19%)	3 (38%)	0.148 (F)
Inflammation	14 (20%)	6 (43%)	0.029 (F)	5 (16%)	3 (38%)	0.085 (F)
Primary prevention	36 (52%)	12 (86%)	0.005 (X^2)	n.a.		
monotherapy (vs. dual)	46 (66%)	13 (93%)	0.017 (F)	13 (41%)	3 (38%)	0.587 (F)

Non-steroidal anti-inflammatory drugs were taken by 14 (20.3%) aspirin users, of which 5 patients were prescribed the potentially interfering ibuprofen. Electronic adherence records showed that the actual exposure to that DDI was low, as none of the five patients took ibuprofen more than once during the observed week.

Potentially DDI-causing high doses (≥40 mg) of lipophilic statins were taken by 25 (78%) clopidogrel users. Those 16 patients (50%) with concomitant statin intake were over-represented in the resistant group in comparison to 9 patients (28%) with staggered intake (p=0.027). The DDI with PPIs could not be analysed because only 7 patients (22%) were exposed and only 4 of them took (es-) omeprazole.

A total of 18 (56%) clopidogrel users showed polymorphisms of the CYP2C19 gene. Heterozygous poor metaboliser (PM) genotypes (CYP2C19*2 or CYP2C19*4) were present in 6 (19%) patients, and 10 patients were ultrarapid metabolisers (CYP2C19*17). In two patients, compound heterozygous genotypes (CYP2C19*17 and *2 or *9) with unknown

phenotype association were found. A tendency towards a higher frequency of the poor metaboliser genotypes in resistant patients could not be observed.

Patients were grouped by the presence of presumed factors to resistance and the mean ADPtest differences were calculated to quantify the effect of these factors. With a mean ADPtest difference of 0.3 AU (CI: -18.1 – 18.6; p=0.98), platelet aggregation of CYP2C19*2/*4 poor metabolisers was almost equal to the wild type patients. Mean ADPtest differences of 9.5 AU (CI: -12.5 – 31.5; p=0.38, unpaired t-test) for patients with diabetes and 17.3 AU (CI: -5.7 – 40.3; p=0.14) for patients with inflammation were found when compared to patients without the respective disease factors. The mean ADPtest difference for concomitant vs. staggered intake of $\geq$ 40 mg statin was 16.2 (CI: -5.1 – 37.5; p=0.13). All of the p-values in this section result from unpaired t-tests.

Adherence Measures

All dispensed punch cards were returned at visit 2 (100% return rate). Visual inspection confirmed that all removals were executed (100% taking adherence). Electronic adherence data was missing in 4 patients (3 aspirin users and 1 patient with aspirin and clopidogrel) due to a deficiency in the recording technology, thus timing adherence was evaluable in 78 patients (95.1%). The timing of drug intake in the morning (mean intake time 7:33±1:00 h) and in the evening (19:01±1:35 h) differed significantly regarding intra-individual variability of drug intake (t_{VAR}=34:16min:sec vs. 49:31min:sec; p=0.05, unpaired t-test). The MMAS-8 (median: 8.0; range 4.5-8.0) and the BMQ sub-scores for necessity (20; 6-25) and concerns (8; 5-20) predicted a generally high adherence. No correlation was observed between subjective adherence scores and biomarker measures such as ΔASPItest (MMAS-8: ρ=0.43; p=0.73 and BMQ differential: ρ=-0.002; p=0.99) or ΔADPtest (MMAS-8: ρ=0.112; p=0.54 and BMQ differential: ρ=-0.056; p=0.76).

Discussion

Incidence of Antiplatelet Resistance

The observed incidence rates of 20% resistance with aspirin and 25% resistance with clopidogrel after electronically monitored adherence are in the broad range of previously reported double-digit incidence rates in ambulatory maintenance settings [66, 67]. However, the rates strongly depend on the used definitions, methods and cut-offs. A study with healthy volunteers recently revealed a higher consistency of the results if testing for antiplatelet resistance was performed after repeated daily administration of low-dose aspirin in comparison to testing after exposure to a single dose, especially when using enteric

coated tablets [114]. This finding supports our approach to test for antiplatelet resistance in patients with chronic low-dose aspirin and monitored adherence. The sensitive ASPItest cut-off set at 30 AU identified all patients whose platelet aggregation was outside the reference range (mean±2 standard deviations) of a sample of treated patients, even if it was lower than the aggregation values observed in our pre-study of untreated healthy volunteers (reference range 57-113 AU). A less sensitive cut-off of 57 AU would have identified 7.2% resistant patients with clearly distinct values from responders. The applied cut-off for clopidogrel resistance (53 AU) relied on ADPtest results that were within the reference range of untreated blood donors. Trials aimed at the validation of cut-offs have been performed and rising evidence supports the clinical prediction from modern platelet function tests [19-21]. However, no definite cut-off could be defined under which patients are protected from clinical events. Given the normal bell-shaped distribution of ADPtest results in clopidogrel users and in accordance with the understanding of clopidogrel resistance as a continuous phenomenon, treating ADPtest as a scaled variable may be preferable [115, 116]. The analysis by comparison of mean ADPtest identified the same principal factors (inflammation and diabetes mellitus) to be associated with antiplatelet resistance.

(Non-) Adherence

Inspection of the returned punch cards and electronic records confirmed complete taking and regular timing adherence during study participation. Possibly lower adherence prior to study participation did not translate into ASPItest differences, but may explain the non-significant difference between the ADPtests at visits 1 and 2. Clopidogrel may be less forgiving than aspirin, thus rendering the ADPtest more sensitive to detect non-adherence. However, adherence monitoring did not influence the number of patients that were below the cut-off for resistance.

Our results do not support the same prominent impact of non-adherence which was notably attributed to aspirin resistance in previous reports. In a meta-analysis of 10 antiplatelet prevention trials, non-adherence was suggested to range between 12% to 52% [117]. Cuisset et al. reported a resistance rate of 14% in outpatient aspirin users that was almost completely attributed to non-adherence [66]. Clopidogrel adherence was measured by self-report in the German Stroke Databank and decreased from 81.6% at three months to 61.6% after one year [118]. Serebruany et al. found a non-adherence rate of 22% in clopidogrel users when referring to inactive carboxyl metabolite measurements [67]. The results of these studies suggest a substantial proportion of resistance that would disappear after controlled exposure. However, the inter-individual heterogeneity in the pharmacokinetics of

clopidogrel is well-known and it affects the ability of drug or metabolite measurements for adherence assessment [28]. Thus, the conclusions drawn from these results are limited by the shortcomings of the applied methods, which could be overcome by our study design with prospective multidrug adherence monitoring.

Other Contributing Factors

We could confirm a significant impact of inflammation and diabetes mellitus on platelet inhibition. Both factors have repeatedly been associated with antiplatelet resistance in previous reports [64, 119-121]. Drug-drug interactions with statins, PPI (clopidogrel) and ibuprofen (aspirin) have been analysed in the respective samples. The data collected by POEMS revealed that the exposure with PPI and ibuprofen was much lower than when referring to prescriptions, which rendered analysis unhelpful. Additionally, the precise tracking of the exposure to clopidogrel as well as to the potentially interfering drug allowed identifying the significant impact of concomitant vs. staggered intake of high dose lipophilic statins, which compete with the second step of clopidogrel activation by the CYP3A4 isoenzyme. The interference by lipophilic statins (atorvastatine and simvastatine) has been identified by Lau et al. in retrospective analysis of 47 patients [122]. The results obtained in a prospective trial with a flow-cytometry based assay to measure platelet activation supported these findings with weak but significant influence of statins on clopidogrel effectiveness [108]. Malmström et al. failed to confirm these findings in a prospective trial with randomised allocation of 69 patients to simvastatin, atorvastatin or rosuvastatin [123]. Finally, a large prospective trial with long-term observation further discharged statins from their presumed effect on platelet aggregation [124]. However, none of these trials controlled for adherence, neither to the antiplatelet agent nor to the interfering drug. Given the high prevalence of non-adherence, these methodological shortcomings may dilute the effect of presumed DDIs. The consideration of adherence calls for statistical models to integrate the variability of drug exposure as an independent continuous variable [125]. With the POEMS employed in our study, the concomitant intake of high-dose lipophilic statins could be identified as the most probable factor contributing to clopidogrel resistance.

Polymorphisms of CYP2C19 in clopidogrel users were not directly associated with improved or impaired clopidogrel response. Analysing whether a possible interaction between pharmaco-genetic and clinical factors may explain the phenotype is far beyond the power of our study. In larger studies, the presence of the CYP2C19*2 variant was significantly associated with insufficient antiplatelet response to clopidogrel, while the results regarding CYP2C19*17 were less consistent [103, 126-129].

Strengths and Limitations

The strength of our study lies in the precise assessment of the patients' medication and the close monitoring of patient adherence and exposure to drug drug interactions due to the monitoring with POEMS. In a pre-study on platelet aggregation with healthy volunteers, the manufacturer's cut-offs were verified, and low general aggregability of the platelets was ruled out by TRAPtest. This allowed a reliable classification of the patients according to their ASPItest and ADPtest results which remain, like any other biomarker, imperfect surrogates of the clinical outcomes

One weakness is the recruitment performed by the GPs that did not follow a randomised procedure. A precise number of the approached patients could not be given. All patients whose data were transmitted to the study centre were successfully joined by phone, indicating a probably great motivation and a voluntary study participation which may not represent the average outpatient population. Thus, a possible recruitment bias cannot be excluded. Further inherent limits arise from the small sample size of this explorative study, which did not allow quantifying the impact of each of the contributing factors on platelet inhibition. Additionally, not all presumed factors to antiplatelet resistance were analysed, like e.g. COX-1 polymorphism in aspirin.

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Conflicts of Interest

The authors declare no conflict of interest.

References

See general references section.

4. RESPONSE TO VITAMIN B_{12} SUPPLEMENTATION

4.1. ACCEPTANCE AND BIOMARKER RESPONSE WITH ORAL VS. INTRAMUSCULAR SUPPLEMENTATION OF VITAMIN B_{12} IN PRIMARY CARE

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Study proposal; Study approved (not yet recruiting)

1. Glossary

See general abbreviations section.

2. Project Background

This study was designed in line with a previous study on "antiplatelet resistance with aspirin and clopidogrel" which combined electronic multidrug adherence monitoring with oral solid drug treatment and biomarkers. The underlying concept is that biomarker response in oral drug therapy can be influenced by incomplete adherence to the prescribed drug regimen. Effectiveness in comparison to ideal therapy can be hampered by non-adherence. Electronic monitoring of adherence can be used to rule out or to control for non-adherence. This allows making a difference between behavioral aspects and pharmacological factors for reduced effectiveness in subgroups of patients. The identification of individual factors of non-response is a prerequisite for personalized interventions to improve response in affected patients. The contribution of this project against this background lies in a) the characterization of biomarker response of adherence-controlled oral treatment in comparison to i.m. treatment and b) the investigation of acceptance of the respective administration routes, because low acceptance might constitute a barrier for successful outpatient drug treatment.

3. Project Organisation

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4. Rationale

Biochemically, VB12 deficiency is characterized by subnormal to borderline VB12 values in the serum. Holotranscobolamine (holoTC) is the bioactive form of VB12 and has been discussed as a more specific and sensitive marker of VB12 deficiency. Functional VB12 deficiency is characterized by both an increase of methylmalonic acid (MMA) and/or homocysteine (hcy). Further laboratory findings are hematological abnormalities such as megaloblastic anemia, 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, but no clear-cut limits exist for the prediction of symptoms.

The true prevalence of VB12 deficiency in the general population is unknown, but 15% of adults older than 65 years had laboratory evidence of VB12 deficiency in a population based study [130]. In large US surveys, about 6% of the population aged ≥60 years suffers from VB12 deficiency, whereas closer to 20% of the population have marginal VB12 status in later life [131]. Etiological factors of VB12 deficiency can be divided into nutritional cause [132, 133], malabsorption syndromes and other gastrointestinal causes [132]. Pernicious anemia typically presents with manifest hematological signs and is associated with antibodies to intrinsic factor and/or parietal cells, but will account only for a small proportion of the observed cases of VB12 deficiency in the study population [134]. Furthermore, defective transport mechanisms due to genetic factors account only for a very small proportion of the disease. Drug drug interactions with acid-lowering agents may also play a role in the development of VB12 deficiency [135]. VB12 deficiency can result in hematologic, neurologic and psychiatric manifestation and is associated with a possibly increased risk of myocardial infarction and stroke.

The treatment of VB12 deficiency consists of vitamin B_{12} supplementation, which can be performed either orally or by i.m. injections. In Switzerland, no high-dose VB12 oral mono-preparation is currently available, and VB12 supplementation is almost always performed with i.m. injections of VB12 [136]. Unlike other European countries, high dose oral VB12 is rarely used for the treatment of VB12 deficiency in Switzerland despite that there is reasonable evidence of its effectiveness [137-140]. 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 [141].

In this study, biomarker response after supplementation with oral and intramuscular VB12 preparations will be compared in a randomized clinical trial. Electronic adherence monitoring will be used to control for non-adherence as a possible confounder in oral treatment. Laboratory findings of VB12 deficiency are responsive to treatment. They have specific response dynamics, and therefore qualify for the evaluation of VB12 supplementation.

Oral treatment with VB12 may be superior to i.m. injections in terms of patient acceptance and cost-effectiveness [142]. Apart from the comparison of biomarker response, this study will help to explore the possible benefits of high dose oral treatment with VB12 in a representative population with consideration of adherence issues, patient comfort and cost effectiveness of outpatient treatment.

5. Aims of the Study

5.1. Primary Aims

- To compare the biomarker response of oral vs. intramuscular treatment of VB12 deficiency
- To explore the dynamics of response reflected by various VB12 associated biomarkers
- To compare subjective acceptance in terms of presumed advantage, preferences with oral vs. intramuscular supplementation with VB12 in the view of the patient and the physician

5.2. Secondary Aims

- To assess the rate of laboratory-confirmed deficiency in patients selected by their physician for VB12 deficiency screening
- To assess clinical, nutritional and demographic factors associated with VB12 deficiency
- To assess factors which are associated with poor response to VB12 supplementation in general and in the respective groups with oral and i.m. treatment
- To estimate cost-effectiveness of oral supplementation compared to intramuscular injections

6. Hypothesis

We hypothesize that…

- …patients with oral treatment of VB12 deficiency are not less prone to have normalized levels of VB12 associated biomarkers than patients with i.m. treatment over the treatment period of 4 weeks.
- …early biomarker response after week 1 and 2 is predictive of the normalization of VB12 levels after 4 weeks of treatment. Low responders at week 1 and 2 are less likely to reach therapeutic targets at week 4.
- …VB12 levels are more sensitive to VB12 supplementation at treatment initiation, while response of functional parameters of VB12 deficiency is slower.

7. Research Plan

7.1. Study Design

Prospective randomized unblinded parallel group trial. A control group with placebo is not foreseen due to ethical considerations.

7.2. Recruitment

Patients whose physician has ordered a laboratory test for the biochemical confirmation of VB12 deficiency will receive a patient information and informed consent form from the laboratory (Information for the patients; Written informed consent form; Accompanying letter). In the letter, the patients are asked to bring along the informed consent form to their next scheduled visit with their GP, during which the results of the lab test will be discussed. Previously, a member of the study team will contact the patients by telephone to provide additional oral information if necessary, followed by a telephone-based interview if on acceptability (questionnaire Q-A) and on demographics and nutrition (questionnaire Q-DN). Patients with serum cobolamin concentrations < 200 pmol/l in whom supplementation with VB12 should be initiated according to the physician's decision will be asked by their GP to participate in the biomarker study. Patients who give written informed consent will be randomly assigned to the conventional intramuscular treatment, or to the oral treatment group. The oral treatment group will be handed out 28 tablets of 1000 µg cyanocobolamine (B12 "Ankermann"; Wörwag Pharma GmbH & Co, Böblingen, Germany) in a 28 day blister supplied with electronic adherence monitoring, while patients in the conventional i.m. supplementation group will receive weekly injections of 1000 µg cyanocobolamine (Vitarubin® Depot 1000 µg / 1 ml; Streuli Pharma AG, Uznach, Switzerland, mixed with Lidocain 1% 1 ml before injection). The two treatment options will not be blinded, and a control group is not foreseen due to ethical reasons.

Participation in the acceptance study, which basically consists of two questionnaires on acceptance, demographics and nutrition is possible for all patients, regardless of their VB12 test results and not restricted to patients who give informed consent for the biomarker study.

7.3. Inclusion/Exclusion Criteria

Inclusion Criteria

- GP's prescription for VB12 deficiency testing
- Age > 18 years
- Ability to give written informed consent
- Vitamin B_{12} serum concentrations < 200 pmol/l
- and indication for vitamin B_{12} supplementation according to the GP's estimation

Exclusion Criteria

- Patients with concurrent intake of vitamin preparations containing VB12
- Patients with a previously diagnosed dementia
- Patients with known hereditary transcobolamin transportation defects
- Patients with known hereditary defects that might compromise the tolerance to the vitamin B12 "Ankermann" tablets according to the summary of product characteristics (Fachinformation Wörwag Pharma GmbH, September 2009)
- lack of written and/or oral understanding in German, French, Italian or English languages

Patients with laboratory confirmed VB12 deficiencies who qualify for VB12 supplementation will be started with the randomly assigned treatment.

7.4. Study Procedure

Randomisation

Randomized allocation to the oral and i.m. treatment groups will take place after successful inclusion of the patient in the GP's office. Randomisation will be performed in random permuted blocks of four with the help of a randomisation list that will be generated by a statistician that is not involved in the study operation. Subsequently, envelopes containing the information on treatment allocation will be delivered to the recruiting physicians in multiples of four according the block size. The information will be numbered from 1-60, and the physician is asked to open the subsequent envelope for each patient who has been

successfully recruited. Stratification groups will not be applied in the randomisation procedure, because there is no evidence for inhomogeneous response between different patient groups (e.g. sex, age, diagnosis). Rejection of the randomly assigned treatment group will not be possible. If a patient is unwilling to accept the assigned treatment, study participation is not possible and the treatment will be assigned to the next eligible patient.

Disposition and Initialization of Treatment

Standard i.m. treatment will be provided directly in the physician's office by the treating physician. Oral VB12 treatment will be provided to the physician in blisterpacks with 28 cavities, equipped with the electronic monitoring system, after production at the study center by a trained pharmacist. After allocation of a patient to the oral treatment group, a patient label will be affixed to the 28-cavity blister and electronic adherence monitoring will be initialized. A member of the study team will be in charge to dispense the blister for oral treatment and explain to the patient how this device should be used on the same day.

Treatment Plan

- Oral VB12 group: daily intake of 1 dose of 1000 μg cyanocobolamine from day 0 to day 27
- VB12 i.m.: weekly i.m. administration of 1000 μg cyanocobolamine (day 0, 7, 14, 21)

VB12 Treatment Monitoring

Patients who gave written informed consent will start with the randomly assigned treatment at their next scheduled visit with their physician. On the first day of treatment (day 0), a baseline blood sample will be drawn before the first intake of oral VB12 or i.m. application.

Further blood sampling will be scheduled according to Tab. 1 and response to treatment will be measured with a panel of VB12 associated biomarkers (holoTC, Hcy, MMA).

Table 1. Visit schedules

Visit		Timing	Activity	Site of execution
(S)	Screening	Day -14 to -2	Blood sampling	General practitioner
(V0)	Baseline	Day 0	Inclusion	General practitioner
			Blood sampling	General practitioner (before treatment initiation)
			Randomization and Treatment initiation	General Practitioner
(V7)	2nd visit	Day 7 (+/-1 day)	Blood sampling	Clinical laboratory
(V14)	3rd visit	Day 14 (+/- 1 day)	Blood sampling	Clinical laboratory
(V28)	4th visit	Day 28 (+/- 2 days)	Blood sampling	Clinical laboratory

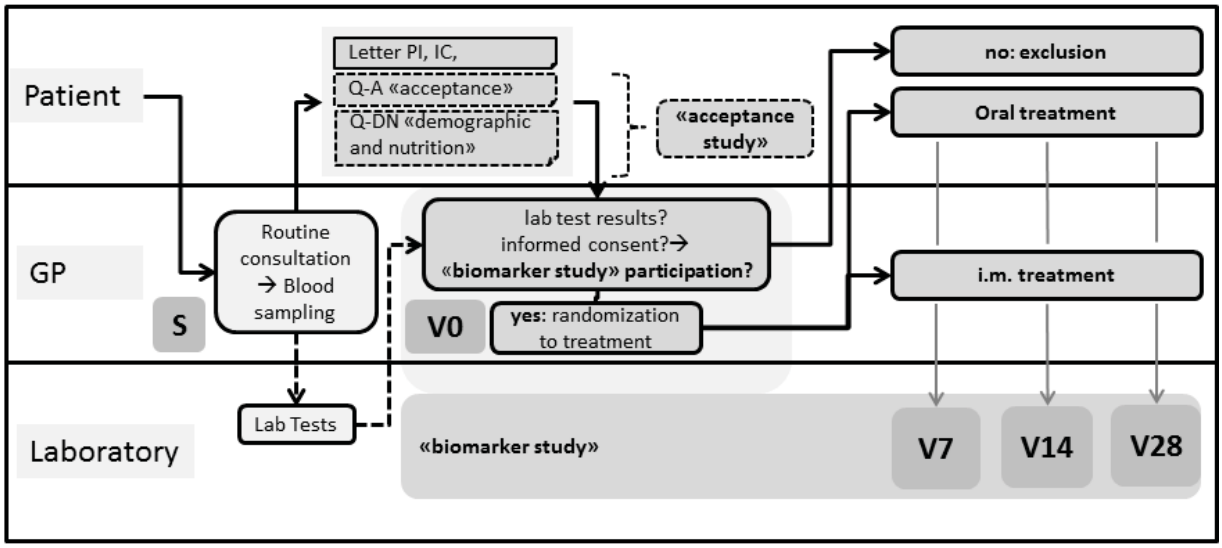

Figure 1: Study flow chart. PI=patient information, IC= informed consent, Q-A=questionnaire "acceptance"; Q-DN=questionnaire "demographics and nutrition". S, V0, V7, V14, V28 → see Tab. 1.

7.5. Outcome Measures

Primary Outcome Measures

- VB12 levels and VB12 associated biomarkers holoTC, Hcy, MMA **at visits V7, V14, V28**
- Patient's answers to questionnaires on subjective acceptance of oral vs. i.m. treatment

Secondary outcome measures

- Electronic adherence parameters VB12 tablets once daily
- Rates of laboratory-confirmed VB12 deficiency in samples sent for VB12 screening **(S)**
- Patient's answers to questionnaires on clinical, nutritional and demographic factors
- Estimated cost-effectiveness of oral supplementation

7.6. Data Collection

Table 2. Data collection

Timing *(referring to Tab. 1)*	**Form / Procedure**	**Filled in… / reported by…**	**Examples of measures**
Screening **(S)**	Laboratory prescription	GP	
	Laboratory Report	Clinical laboratory	Lab test results
Before **V0** (baseline visit)	Informed Consent	Patient; signed by patient and investigator at V0	Signed informed consent
Before randomization to treatments	Q-DN: "demographics and nutrition"	Patient	Patient characteristics
			Nutritional habits, clinical characteristics
	Q-A: "acceptance"		Acceptance of oral and i.m. treatment
Baseline visit **(V0)**	Inclusion and Randomization	GP	Decision for treatment; if yes randomized allocation to treatment group
	Laboratory prescription		Baseline laboratory
	Q-GP: physicians questionnaire		Pre-existing diagnosis
Study centre visits **(V7, V14, V28)**	Lab report: VB12 associated biomarkers	Clinical Laboratory	Baseline and biomarker response under therapy
Final visit **(V28)**	Adherence Report	Read out data at Clinical Laboratory	electronic adherence parameters

7.7. Data Analysis

Collected data will be verified and checked for plausibility by the co-investigator or a trained member of the study team. Relevant data for analysis will then be entered into the study database with the following sections: Patient characteristics, clinical data with co-medication, laboratory data, and adherence data. Descriptive statistics will be performed to characterize the study sample. The data will then be analyzed for presence of significant

differences in biomarker response between the two treatment groups, and sub-analysis of the data will allow assessing factors that are associated with response to treatment. Furthermore, associations between adherence data and response with oral treatment will be explored.

8. Expected Results

We expect to find laboratory evidence of VB12 deficiency in approximately 30% of the samples sent for confirmation from general practitioners surgeries. In addition we expect to confirm that borderline and deficient VB12 levels go in parallel with eleveated levels of homocystein, thus supporting diagnostic strategies that rely on homocystein and/or MMA when VB12 results are inconclusive.

Biomarker response to supplementation is expected to be equally effective in both treatment groups. First signs of response with biochemical markers are expected to be present after 1-2 weeks of treatment independently of the way of administration. They should be predictive for long-term biomarker response after 4 weeks of therapy initiation. Non-adherence is expected to be a rare issue in a study with voluntary participation and electronic adherence monitoring. Thus, we will not be able to study the impact of non-adherence on the dynamics of biomarker response. This crucial issue in oral outpatient medication should be addressed in a follow-up study evaluating the possible impact of adherence aids, if the current study can verify non-inferior biomarker response of adherence-confirmed oral treatment in comparison to i.m. VB12 supplementation. Given the choice between oral and i.m. treatment, most patients are expected to prefer the treatment by the oral route.

9. Sample Size and Statistics

60 consecutive patients with a newly diagnosed or recurrent, but currently untreated VB12 deficiency sent from recruiting GP's to the laboratory for VB12 testing will be integrated in the study on biomarker response with oral vs. i.m. treatment. The accompanying study on subjective acceptance of the two treatment options will be performed until the aim of 60 patients with evaluable data in the biomarker response study is reached.

9.1. Statistical Considerations

The primary aim of this parallel group trial is to show that oral VB_{12} supplementation (daily intake of 1000 µg cobalamin) is not inferior to intramuscular supplementation (weekly injection of 1000 µg Cobalamin) in terms of serum cobalamine and homocystein

concentrations within the first month of treatment. The response to both treatment options is presumed to be homogenous irrespective of age, sex and diagnosis, and stratification is not presumed to be necessary.

Outcomes in terms of serum cobolamin and homocystein concentrations after 4 weeks of treatment are presumed to be normally distributed in both groups and treatment groups, and groups will have nearly the same size due to block randomization.

Serum cobolamin and homocystein concentrations can be corrected within the first few weeks of supplementation. A randomized trial with oral vs. intramuscular treatment showed superior results after 4 months with oral vitamin B_{12}, but successful demonstration of non-inferiority is likely to be possible within 1 month (see Fig. 1 and 3 in Reference) [143]. Although the therapeutic regimen and the presumed baseline vitamin B_{12} concentrations are slightly different, the trial of Kuzminski et al. has served as a template for the following sample size estimation. In contrast to published randomized trials, additional blood sampling after week 1 and 2 will be more effective to collect data on short term biomarker response [137]. However, sample size estimation for this study is based on assumptions regarding outcomes after 4 weeks. Patients are presumed to display baseline cobolamin concentrations of 100 – 150 pmol/l. Based on published data, which is in line with the experience in our own lab, patients reach levels of approximately 600 pmol/l, with an estimated standard deviation of 120 pmol/l (CV=20%). A maximum difference of 100 pmol/l will be accepted between mean intramuscular and oral supplementation to accept non-inferiority of the latter, because this difference to be a clinically meaningless difference.

Given the above assumptions and if there is truly no difference between the groups with intramuscular and oral supplementation, then 50 patients are required to be 90% sure that the lower limit of a one-sided 95% confidence interval will be above the non-inferiority limit of -100 pmol/l (α = 5%; power (1 – β) = 90%).

This result has been calculated based on the formula: $n = f(\alpha,\beta) \times 2 \times \sigma^2 / d^2$ where σ is the standard deviation and d the tolerated difference to accept non-inferiority. This simplified but valid procedure for sample size calculation has a tendency to slightly underestimate the required sample size [144]. To minimize the risk of an underpowered trial, the inclusion of 10 additional patients with evaluable data seems justified.

9.2. Statistical Analysis

Statistical analysis will be performed with all complete datasets that could be collected during the trial. The hypothesis regarding the biomarker response with oral and

intramuscular VB12 supplementation will be tested with a one-sided t-Test for cobolamin concentrations and VB12 associated biomarkers such as MCV, percentage of hypersegmented neutrophils, holotranscobolamin and homocystein.

The predictive value of the early biomarker response after 1 and 2 weeks of treatment will be tested with a rank correlation test for paired samples with prior correction for the baseline variation.

For the evaluation of the acceptability of the two treatment options, the frequency of patient's answers to questionnaire Q-A will be calculated. The relative frequencies of answers in specific patient groups (e.g. males, patients > 60 years) will be compared and statistically tested if descriptive analysis suggests a clustering of the data.

The number of laboratory confirmed deficiency (deficiency: serum cobolamin < 150 pmol/l , grey zone: 150 – 220 pmol/l) will be put into relation to the number of patients with suspected vitamin B_{12} deficiency. Patient characteristics (demographic data, diagnosis, nutrition) will be compared between patients with and without confirmed vitamin B12 deficiency.

If the descriptive analysis reveals evidence for inhomogeneous response to VB12 supplementation in the study population, an analysis for factors associated with low response will be performed. Up to now there is no evidence for an impaired response in specific patient groups.

10. Patient Information

Patients with a proposal for VB12 testing will be informed about the study by a letter with written patient information and informed consent form. All patients will be informed about their routine laboratory results irrespective of study participation. Study participants will be informed about their performance regarding biomarker response with VB12 supplementation at the final visit (V28). The results are submitted to the recruiting GP. If the results at the end of study participation show that a patient is unlikely to reach the desired long term response, alternative drug regimen or diagnostic procedures in order to reach the therapeutic goals will be discussed with the referring physician and proposed to the patient upon the next scheduled routine consultation.

11. Institutional Review

The study will be carried out according to Swiss law and in consistence with the Declaration of Helsinki. The study will be submitted to and approved by an independent ethical

committee of the Cantons of Aargau and Solothurn. Registration of the study centre (=clinical laboratory) will be applied for by the local authorities (Kantonsapothekeramt Solothurn, Dr. pharm. Marco Schärer) and the study will be registered at ClinicalTrials.gov. Furthermore, the notification of the study will be proposed to the clinical trials section of Swissmedic.

12 Safety Issues

12.1. Safety Considerations

Patients who participate in the study will not be exposed to drugs other than they would receive if they were tested and supplemented with VB12 in a standard care setting. The difference to standard care consists in the standardized administration of i.m. injections and standardized schedules for response evaluation with biomarker measurements, and in the route of administration in patients who receive oral VB12. Patients with oral treatment are not expected to experience more adverse events than patients with i.m. VB12 supplementation. Oral treatment with adherence monitoring is unlikely to be less effective than i.m. injections. However, if a patient does not adequately respond to oral treatment, this will be disclosed by the laboratory evaluations and can be corrected by therapeutic and diagnostic measures mentioned in section #10 after study participation.

Oral drug disposition in electronically monitored blister packs is not known to constitute a risk for participants, since it does not differ from other drug blisters packs and its use will be demonstrated carefully. Blister pack preparation will be carried out by pharmacists with the help of techniques commonly used in pharmacies to optimize safety in drug dispensing. The risks concerning laboratory assessment will be limited to those associated with blood sampling, which does not differ from routine blood sampling for in vitro diagnostics. Venous blood withdrawal can lead to malaise, vertigo and faint (rare). At the site of venipuncture, redness, pains, swelling, blue spots and – infrequently – infection may occur.

12.2. Adverse Drug Reaction Reporting

Serious adverse events (SAEs) will be reported by the principal investigator to the local ethics committee within 7 days with the SAE form. Events classified as suspected unexpected serious adverse reaction (SUSAR) will be reported by the Sponsor-Investigator both to swissmedic and confirmed to the local ethics committee with the CIOMS form within 7 days.

The occurrence, treatment and monitoring of non-serious adverse events that are in line with the summary of product characteristics of the IMPs will be documented. A summary of

these reports will be integrated in the annual safety report of which copies will be sent to the local ethics committee and to swissmedic each year and after study completion.

13. Patient Confidentiality and Data Protection

All patient information obtained as a result of the study will be regarded as confidential. Clinically relevant results will be transmitted to the referring GP. For data processing, results will be made anonymous using a unique study ID number instead of name and surname of the patient as soon as identification of the subject is not required any more. The patient identification key and the randomisation code will be stored in a separate excel file with password protected access.
Digitised data will be stored in the study centre on a network resource. Access will be limited to the study team only.
The informed consent form will be archived by the investigator in the study centre together with the case report forms (GP's report form, patient's questionnaires, and laboratory test results) in a cupboard accessible only for the investigators.

14. Disclosure of Data and Publication

All information obtained in the context of this study will be regarded as confidential, at least until the appropriate analysis and review by the principal investigators are completed. For publication, first author will be Philipp WALTER, last author will be Kurt E. HERSBERGER and in between in undefined order other colleagues who will have made important contributions to this project, first of which are – corresponding to the current project team composition – Cyrill JEGER and Isabelle ARNET.

15. Funding

At the moment of submission, the funding is provided by the research group (Pharmaceutical Care Research Group). The involved laboratory (Aarelab, Olten) will provide facilities for blood sampling, laboratory infrastructure and will support patient recruitment and study operation. Pharmis GmbH (Beinwil a.S., Switzerland) will provide blisters to dispense oral VB12. The electronic adherence monitoring technology will be obtained from the Confrérie Clinique, CH-Lausanne (ECCT B.V., Eindhoven, NL). The investigators will inform the ethics committee if funding will be completed by an industrial sponsor.

16. Appendices

No appendices

17. References

See general references section.

5. GENERAL DISCUSSION

In this thesis, we developed a new approach towards the investigation of drug resistance. The burden of drug resistance with cardiovascular medication – notably lipid lowering drugs and antihypertensives – was estimated in **project A** from the rate of patients who failed to attain their presumed biomarker target values. In this first study, we found that therapeutic targets of lipid lowering therapy and antihypertensive therapy were missed by 25.8% and 36.3% of the patients. Multiple factors may contribute to these impressive rates of patients who apparently fail to take full advantage of the prescribed regimen. Non-adherence is presumably a prominent contributor which merits consideration in any attempt to enlighten the gap between expected and observed biomarker response. Consequently, we developed a generic approach to study drug resistance in **project B** and adapted it to antiplatelet resistance with aspirin and clopidogrel. The design of the study involved the recruitment setting, study procedures, biomarker assessments and the development of the POEMS technology. The combination of electronic adherence monitoring and biomarker measurement allowed evaluating inadequate drug response in the light of drug intake characteristics of the patients. This approach was set up as a model to uncover contributions determined by the patients' disease state or genetic conditions and contributions that may arise from suboptimal execution of the therapy plan. The comprehensive assessment of this variety of factors is a prerequisite for tailored interventions in a truly personalised approach.

The study protocol required the participants to bring all their oral drugs to the study centre. Reconciliation between prescribed drugs and actual therapy helped to solve discrepancies either with the patient or by contacting the prescribing physician. Often, the physicians' drug record was not up to date with the patients' current medication. If we were unable to resolve discrepancies, the patient was advised to take the drugs the way he was used to. According to the study design, adherence monitoring involved both electronic monitoring and directly observed therapy (DOT) in the case of an insufficient biomarker response. This measure to rule out non-adherence in patients who removed the drug from the blister, but discarded it afterwards was not feasible, because patient acceptance was low and the potential small increase of data quality did not justify the high burden on study personnel. Moreover, such irrational behaviour is unlikely in these patients with voluntary study participation, thus DOT was not included in the data analysis.

The *ad hoc* preparation of the multidrug blister was the most time-consuming step in on-site patient management, but could be well integrated in the workflow. Modifications of the therapy plan after reconciliation and dosing instructions after preparation of the patient visit

caused a lot of extra-work. Immediate database updates and proper detailed documentation was critical to obtain reliable data, because this was hard to correct retrospectively. The same is true for the validation of adherence data. Immediate data clearing of raw data at the time of acquisition in front of the patient is inevitable for its verification. A data display / entry system that facilitates real-time data inspection and documentation would be of great value in order to produce high quality data with reduced time effort.

In **project C1**, we used the adherence data collected with POEMS for a sub-analysis exploring the relationship between subjective and objective adherence parameters and their association with biomarkers reflecting the effectiveness of lipid lowering therapy. Most of the patients with a prescription for aspirin or clopidogrel, which was an inclusion criterion of the parent study, received a lipid lowering drug. Timing adherence with lipid lowering drugs is not known to be especially critical for therapeutic effectiveness. However, LDL-C was more closely associated with the time variability of the lipid lowering drug intake than with morning vs. evening intake. The finding that timing precision is generally better in the morning than in the evening may have consequences for drug prescription. Other than in retired patients, the weekend effect with a higher than average contribution to time variability should be considered in working patients. This delay on weekends merits consideration when patients receive drugs for which a precise timing of adherence is required. Constant intervals between doses can help to keep fluctuations of drug concentrations in body fluids low. Whether fluctuations induced by interval length variability are relevant depends on the pharmacologic properties of the compound. However, our results with lipid lowering drugs showed an association between the time variability of drug intake and LDL-C values even though timing adherence is not known to be especially critical for statin therapy. However, such studies have never been performed before and they would be of great value for other drugs, especially for presumably non-forgiving drugs.

We could demonstrate that POEMS is a suitable tool to collect comprehensive data on multidrug adherence with oral solid drugs. Descriptive statistics on median intake time and time variability of drug intake as well as dosing intervals gave insights on the execution of prescriptions in daily practice. It was beyond the scope of this sub-analysis to draw conclusions on the clinical consequences of the observed intake behaviour. Future projects could employ the technology in a patient cohort with prescriptions for drugs where timing adherence is known to be critical for therapeutic efficacy (e.g. antiretroviral drugs for the treatment of human immunodeficiency virus. However, the findings from our study confirm that i) data acquisition with the help of the POEMS technology in an outpatient setting is feasible and ii) significant relationships between objective adherence parameters and

intermediate outcomes (biomarkers!) can be found. The results from this exploratory study encourages to introduce multidrug adherence monitoring to optimize adherence through targeted interventions on one hand and drug development in order to tolerate deviations from ideal executions of drug prescriptions on the other hand.

In **project C2**, we describe the case of a study participant whose irrational drug intake behaviour could be detected and described by multidrug adherence monitoring. A pharmacists' intervention helped to improve objectively measured adherence parameters during the follow-up with effects on the biomarker level and potentially on clinical outcome.

Project D represented the execution of the main study. To our knowledge, this was the first study on antiplatelet resistance in outpatients which prospectively controlled for adherence. Unlike proposed by previous reports based on different measures of aspirin exposure, our results did not confirm that aspirin resistance was mainly attributable to non-adherence [66, 145, 146]. Resistance with aspirin was significantly associated with diabetes mellitus, but mean platelet aggregation was not (aspirin) or only moderately and non-significantly (clopidogrel) influenced by adherence monitoring. In the patient sample with clopidogrel, we observed a continuous distribution of platelet aggregation, which confirmed the expected large intra-individual response variability. Adherence monitoring allowed to precisely measuring the exposure to DDIs that were presumably associated with impaired response. Without precise tracking of the antiplatelet agent and the co-medication, we would not be able to measure the effect of the statin-clopidogrel interaction.

The multifactorial background of antiplatelet resistance with aspirin and clopidogrel has been confirmed by clinical, pharmacological and *in vitro* data and is beyond debate. However, the contribution of non-adherence or imprecise dosing was only measurable with electronic adherence monitoring, which has not been done before. Given the irreversible action of aspirin and clopidogrel on their respective targets, both drugs are presumed forgiving drugs with once daily dosing irrespective of their pharmacokinetic properties. Daily aspirin doses lower than 100 mg can sufficiently suppress platelet thromboxane productions in healthy subjects [147]. In situations with limited adherence, reducing the dose beyond this standard dose may result in an impairment of its antithrombotic efficacy [148]. When platelet turnover is increased, higher doses or shortened dosing intervals may be required to compensate for the shortened forgiveness of antiplatelet drugs [121]. The pathogenetic role of increased platelet turnover in systemic inflammation and diabetes is not definitely clear, but poses a plausible background for antiplatelet resistance under these circumstances.

This study was designed against the background of a concept of personalised medicine that mainly focused on the prediction of safety and efficacy from biochemical and genetic markers of the treated patient. Considering the bio-psycho-social background of the human nature, we tried to integrate factors associated with the patients' capacity to comply with the prescribed therapy plan in a model to measure the respective impact on outcomes. Neither adherence nor pharmaco-genetic factors, but inherent clinical conditions were the strongest predictors of resistance in this study. This finding underlines the need to consider all – behavioural, clinical *and* genetic – factors in the assessment of resistance.

In summary, the execution of projects C and D allowed to collect very helpful results and experiences with the new technology to measure and display timing adherence with a polymedication regimen in daily life. Essentially, the re-packaging of the patients drugs into the multidose punchcard and the electronic registration of drug intake time were well accepted by the patients. Contrary to directly observed therapy (DOT) with a high burden on patient and study personnel, patients did not feel "over-controlled" or hindered in their daily activities by the electronic adherence measurement. Thus, POEMS represented an efficient tool to collect reliable and objective adherence data.

We therefore promote the use of POEMS in **project E**. In a comparison of biomarker response with oral vs. intramuscular injection of vitamin B_{12}, the efficacy of oral administration of vitamin B12 may be diluted by impaired adherence in an intention-to-treat analysis. Controlling for adherence is essential to bring out the true efficacy of oral vitamin B_{12} substitution.

The major challenges during this thesis were:

- To define drug resistance in the context of non adherence
- To establish the scientific support for this multidisciplinary approach to drug resistance
- To elaborate the study design and methods to analyse the data
- To design and to adapt the electronic adherence monitoring in collaboration with Confrérie Clinique B.V., Veldhoven, The Netherlands
- To find adequate methods to process data collected by electronic adherence monitoring and to link them with characteristics of the therapy plan for a comprehensive analysis
- To successfully promote patient recruiting by general practitioners in an ambulatory setting

Limitations

While our approach towards the investigation of drug is generic and can be applied to various drugs and settings, the obtained results are specific for an area in Switzerland where patients receive many of their prescribed drugs from their self-dispensing physician, not from the pharmacy.

Due to technological deficiencies of this first generation of POEMS devices, we failed to register all adherence events. However, there were only 4 patients with completely missing adherence data. In other patients, single events were missing, but did not affect the calculation of summary statistics of objective adherence parameters.

This thesis was not supported by 3rd party funding despite multiple attempts to find industrial partners. This may in part because the investigated lead drugs either have just run out of patent protection (clopidogrel) or have been generic for many decades (aspirin). On the other hand, awareness of adherence issues are lacking and non-adherence seems still a neglected field in the research and development units of many pharmaceutical companies.

6. CONCLUSION

In conclusion this thesis showed that the investigation of antiplatelet resistance by the application of this unique approach with prospective adherence monitoring to all oral solid drugs is feasible. We were able to characterise the temporal pattern of drug intake and found associations between the timing variability of drug intake and attained LDL-C levels in patients with lipid lowering therapy. Considering antiplatelet therapy, we found resistance rates of 20% (aspirin) and 25% (clopidogrel), which is in the range of previous reports. The actual exposure to DDIs was lower than according to prescriptions. We could analyse the timing effect of the DDI between clopidogrel and lipophilic statins and found results that supported staggered versus concomitant intake of these potentially interfering drugs.

Unlike directly observed therapy, POEMS for adherence monitoring during one week was well accepted by the study participants. Disease factors were mainly associated with antiplatelet resistance, whereas non-adherence was discharged from being a major contributor in this outpatient sample.

The following conclusions could be drawn:

- The POEMS technology allowed collecting data on multidrug timing adherence which has not been reported before.
- The new technology and procedures were well accepted by the patients.
- Objectively measured timing adherence parameters are suitable to describe intake characteristics of a patient. Significant deviations from prescribed drug intake can be observed, and intake characteristics vary in different patients' groups.
- The combination of the weekly multidrug blister together with the electronic adherence monitoring was effective to rule out non-adherence.
- The association between the time variability of the LLD intake and LDL-C levels suggests an impact of timing adherence on statin effectiveness
- Antiplatelet resistance in outpatients with maintenance doses of aspirin and clopidogrel is common. Approximately 20% of patients with aspirin and 25% of the patients with clopidogrel are affected.
- Aspirin resistance is rather a dichotomous phenomenon, while platelet aggregation with clopidogrel is a continuously distributed measure.

Our recommendations for daily practice are:

- If there is doubt about the effectiveness of the treatment with aspirin or clopidogrel, the investigation by specific in vitro platelet aggregation tests is recommended. If the test result does not comply with the expected inhibition of platelet aggregation, the further investigation should involve multidrug adherence monitoring to rule out non-adherence and to measure the exposure to potentially interfering drugs. If the insufficient inhibition of platelets persists after one week of multidrug adherence monitoring, measures should be taken to optimize antiplatelet therapy. In the case of clopidogrel, CYP2C19 genotyping should be part of the workup. Comprehensive consideration of the test results, together with medication and clinical data should allow finding alternative treatments to prevent the patient from the potential clinical consequences of antiplatelet drug resistance.
- Multidrug adherence measurement may serve as a useful diagnostic tool to disclose the timing adherence pattern of patients with polymedication. The adherence report is useful to visualize the adherence pattern and may serve as a useful background to discuss timing adherence issues together with the patient.

Recommendations for future research and development:

- Elaboration of the background for a consensual and stringent definition of "drug resistance"
- Development and integration of data on drug adherence into statistical models in order to prevent the dilution or masquerade of effects by the variability of drug exposure
- Study the clinical tolerability of specific drugs towards variability of drug exposure
- Comparison of drug effectiveness with adherence monitoring as an independent variable (e.g. oral vs. intramuscular VB_{12} substitution)
- Design of studies specifically aimed at measuring (intermediate) outcomes of drugs for which timing adherence is critical
- Software development for facilitated analysis and interpretation of timing adherence data

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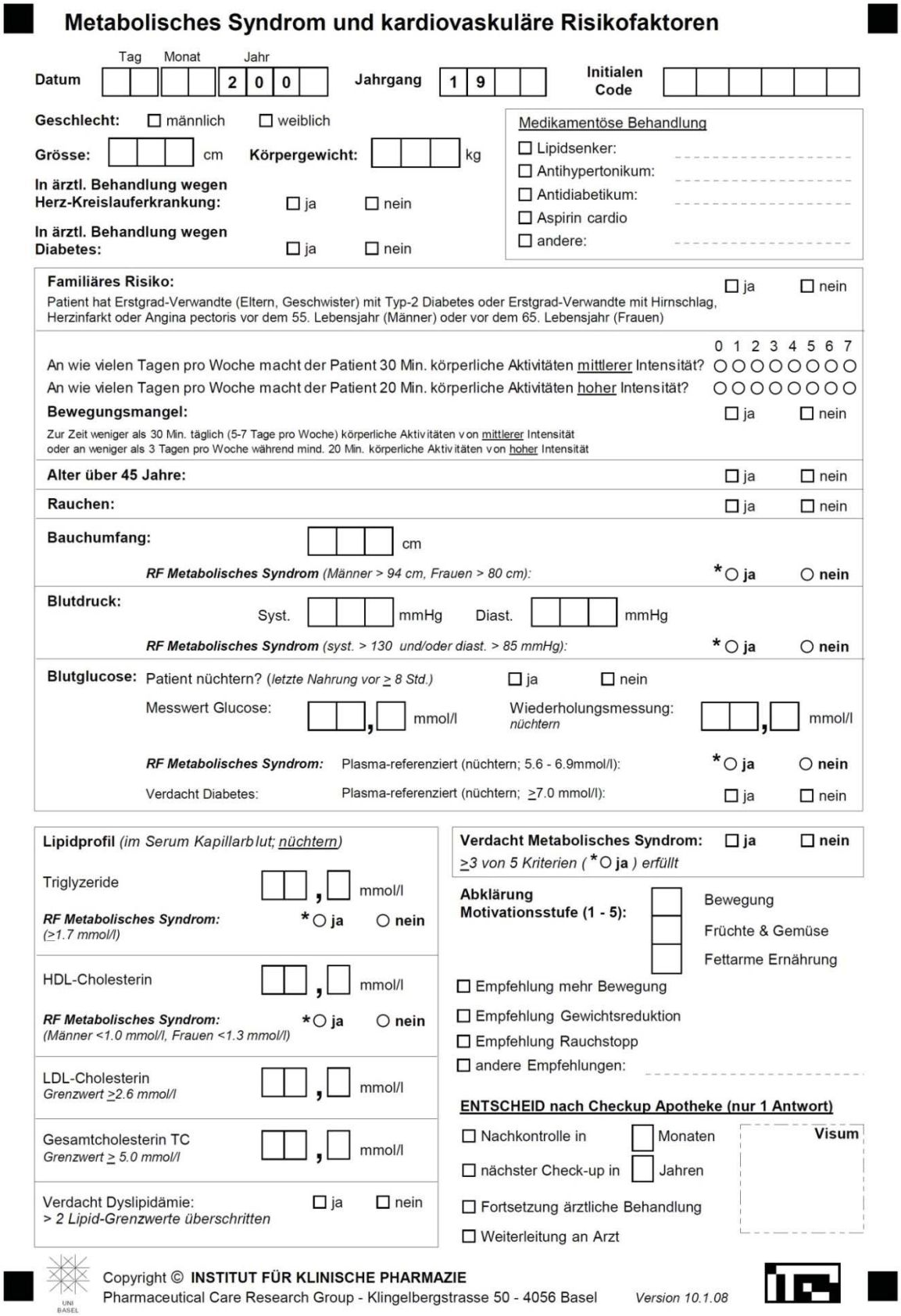
8. APPENDIX

Project A

Projects C and D

Project E

8.1. DATA REPORTING FORM OF THE HERZCHECK® CAMPAIGN 2008



Metabolisches Syndrom und kardiovaskuläre Risikofaktoren

Datum (Tag / Monat / Jahr): 2 0 0 — Jahrgang: 1 9 — Initialen Code

Geschlecht: ☐ männlich ☐ weiblich

Grösse: cm — Körpergewicht: kg

In ärztl. Behandlung wegen Herz-Kreislauferkrankung: ☐ ja ☐ nein

In ärztl. Behandlung wegen Diabetes: ☐ ja ☐ nein

Medikamentöse Behandlung
- ☐ Lipidsenker: _____
- ☐ Antihypertonikum: _____
- ☐ Antidiabetikum: _____
- ☐ Aspirin cardio
- ☐ andere: _____

Familiäres Risiko: ☐ ja ☐ nein
Patient hat Erstgrad-Verwandte (Eltern, Geschwister) mit Typ-2 Diabetes oder Erstgrad-Verwandte mit Hirnschlag, Herzinfarkt oder Angina pectoris vor dem 55. Lebensjahr (Männer) oder vor dem 65. Lebensjahr (Frauen)

0 1 2 3 4 5 6 7

An wie vielen Tagen pro Woche macht der Patient 30 Min. körperliche Aktivitäten mittlerer Intensität? ○ ○ ○ ○ ○ ○ ○ ○

An wie vielen Tagen pro Woche macht der Patient 20 Min. körperliche Aktivitäten hoher Intensität? ○ ○ ○ ○ ○ ○ ○ ○

Bewegungsmangel: ☐ ja ☐ nein
Zur Zeit weniger als 30 Min. täglich (5-7 Tage pro Woche) körperliche Aktivitäten von mittlerer Intensität oder an weniger als 3 Tagen pro Woche während mind. 20 Min. körperliche Aktivitäten von hoher Intensität

Alter über 45 Jahre: ☐ ja ☐ nein

Rauchen: ☐ ja ☐ nein

Bauchumfang: cm
RF Metabolisches Syndrom *(Männer > 94 cm, Frauen > 80 cm):* *○ **ja** ○ **nein**

Blutdruck: Syst. mmHg Diast. mmHg
RF Metabolisches Syndrom *(syst. > 130 und/oder diast. > 85 mmHg):* *○ **ja** ○ **nein**

Blutglucose: Patient nüchtern? *(letzte Nahrung vor ≥ 8 Std.)* ☐ ja ☐ nein
Messwert Glucose: , mmol/l — Wiederholungsmessung: *nüchtern* , mmol/l
RF Metabolisches Syndrom: Plasma-referenziert (nüchtern; 5.6 - 6.9mmol/l): *○ **ja** ○ **nein**
Verdacht Diabetes: Plasma-referenziert (nüchtern; ≥7.0 mmol/l): ☐ ja ☐ nein

Lipidprofil *(im Serum Kapillarblut; nüchtern)*

Triglyzeride , mmol/l
RF Metabolisches Syndrom: *(≥1.7 mmol/l)* *○ **ja** ○ **nein**

HDL-Cholesterin , mmol/l
RF Metabolisches Syndrom: *(Männer <1.0 mmol/l, Frauen <1.3 mmol/l)* *○ **ja** ○ **nein**

LDL-Cholesterin *Grenzwert ≥2.6 mmol/l* , mmol/l

Gesamtcholesterin TC *Grenzwert ≥ 5.0 mmol/l* , mmol/l

Verdacht Dyslipidämie: ☐ ja ☐ nein
> 2 Lipid-Grenzwerte überschritten

Verdacht Metabolisches Syndrom: ☐ ja ☐ nein
≥3 von 5 Kriterien (○ **ja**) erfüllt*

Abklärung Motivationsstufe (1 - 5):
- Bewegung
- Früchte & Gemüse
- Fettarme Ernährung

- ☐ Empfehlung mehr Bewegung
- ☐ Empfehlung Gewichtsreduktion
- ☐ Empfehlung Rauchstopp
- ☐ andere Empfehlungen: _____

ENTSCHEID nach Checkup Apotheke (nur 1 Antwort)
- ☐ Nachkontrolle in Monaten
- ☐ nächster Check-up in Jahren
- ☐ Fortsetzung ärztliche Behandlung
- ☐ Weiterleitung an Arzt

Visum

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Pharmaceutical Care Research Group - Klingelbergstrasse 50 - 4056 Basel *Version 10.1.08*

8.2. LOCAL ETHICS COMMITTEE APPROVAL

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 !

2 / 3

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)

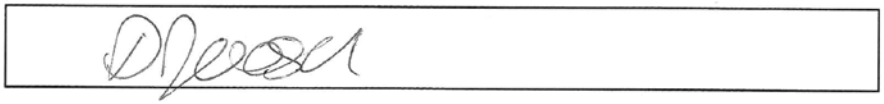
Die Gebührenerhebung richtet sich nach § 4a Abs. 1 lit. a) der Verordnung über die Gebühren in den Bereichen Gesundheit, Soziales und Zivilschutz (Gebührenverordnung) vom 10.6.1991 (Stand 1.10.2005).

Für die Ethikkommission:

Ort, Datum: Aarau, 30. Juni 2009

Name: Dorina Jerosch, lic. iur., Vizepräsidentin

Unterschrift(en):



Swissmedic/BAG/SA
MW 1.1.2002

3 / 3

Philipp Walter, dipl. pharm.
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Frohheimweg 12
4603 Olten

Departement Gesundheit und
Soziales
Kantonale Ethikkommission
Bachstrasse 15
5001 Aarau

Aarau, 3. Juli 2009

Empfehlungen

Änderungsprotokoll vom 03.07.2009
(Ref. Nummer KEK 2009/041, Aspirin- und Clopidogrelresistenz)

Sehr geehrte Frau Jerosch

Entsprechend den Empfehlungen der Ethikkommission habe ich die folgenden Änderungen in der Patienteninformation und in der Einverständniserklärung vorgenommen (im Text gelb markiert):

Patienteninformation

- zusätzlich: Seite 1 unten „mündlich" gestrichen entsprechend dem Einwand von Herrn Bachmann (Vorgehen noch nicht entschieden: schriftlich durch PatientIn auszufüllen oder strukturiertes Interview durch Prüfer).
- Seite 3/3: letzter Satz und Angaben von PD Dr. Hersberger gestrichen

Einverständniserklärung

- Dr. Romanens ist als einziger Prüfarzt aufgeführt
- Zusätzlicher Satz bezüglich Resultatübermittlung an Arzt ist aufgeführt
- Satz bezüglich Einverständnis zu erneuter Kontaktierung ersetzt durch unabhängige Befragung (Seite 2 = Rückseite der Einverständniserklärung)

Es sollen keine Daten ins Ausland gelangen, deshalb habe ich diesen Punkt in der Patienteninformation und in der Einverständniserklärung weggelassen.

Ich bitte um Prüfung der revidierten Dokumente.

Mit freundlichen Grüssen

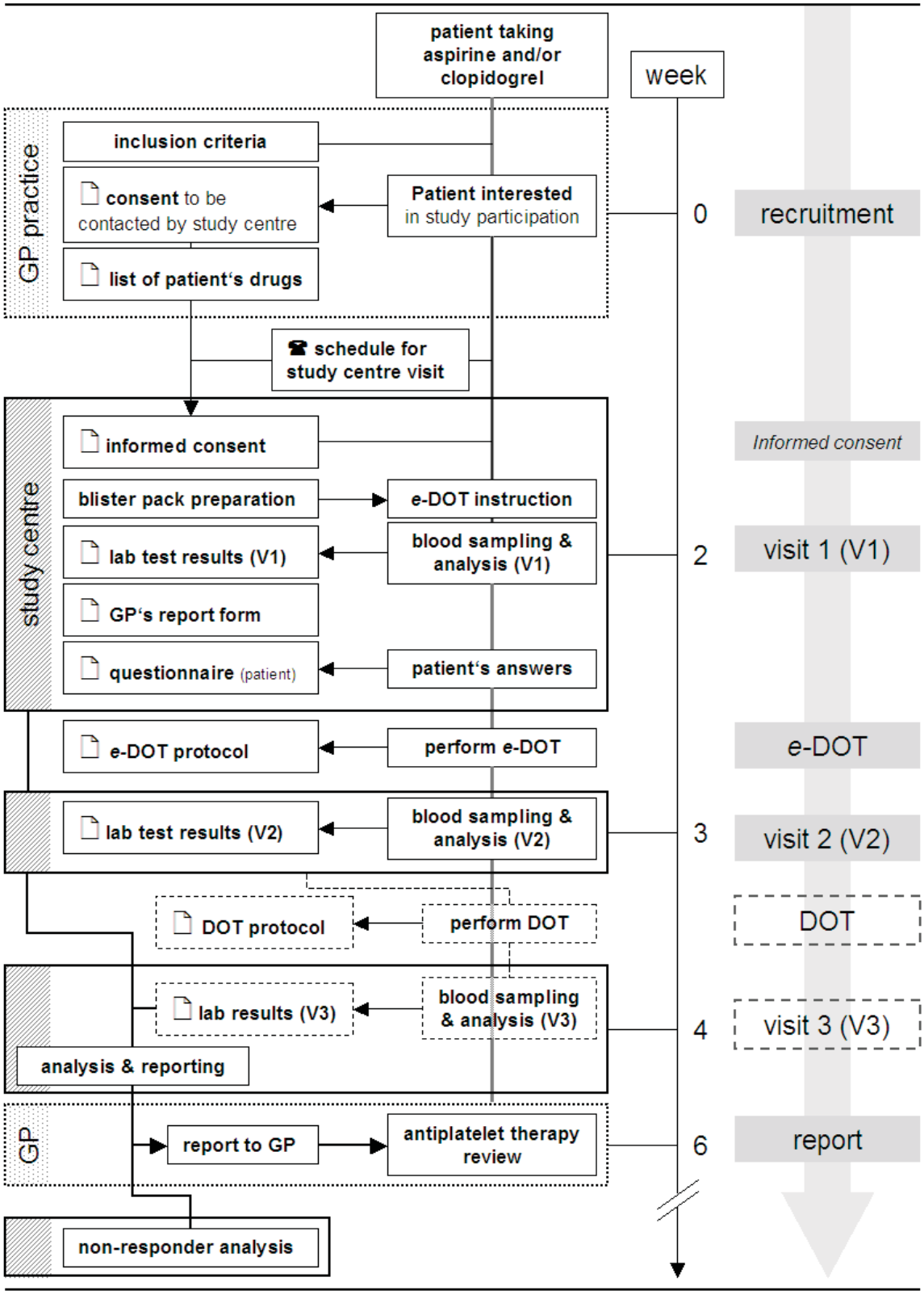
Philipp Walter

Kantonale
Ethikkommission
☑ **Kenntnis genommen**
☐ **Bewilligt**
☐ ohne Auflagen
☐ mit Auflagen gemäss separatem
Schreiben vom .....

Aarau, 27.8.09 **PD Dr. med. O. Hilfiker**
Präsident KEK

O. Hilfiker

8.3. STUDY FLOW CHART



8.4. PATIENT INFORMATION

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

Information

Patientinnen- / Patienteninformation

Verminderte Wirksamkeit von Aspirin Cardio® und Plavix®

Sehr geehrte Patientin, sehr geehrter Patient

Sie sind eingeladen, an einer klinischen Studie teilzunehmen. Bevor Sie sich für eine Teilnahme entscheiden, ist es wichtig für Sie zu wissen, weshalb diese Studie durchgeführt wird und was damit verbunden ist. Das vorliegende Schreiben soll Ihnen diese und weitere Informationen liefern. Für allfällige Fragen oder Unklarheiten stehen Ihnen die am Ende dieses Schreibens aufgeführten Personen gerne zur Verfügung.

Warum wurde ich angefragt?
Sie wurden für die Studie angefragt, weil sie mit Aspirin Cardio® bzw. Generika davon und/oder mit Plavix® behandelt werden. Diese Therapie soll im Rahmen der Studie unverändert weitergeführt werden.

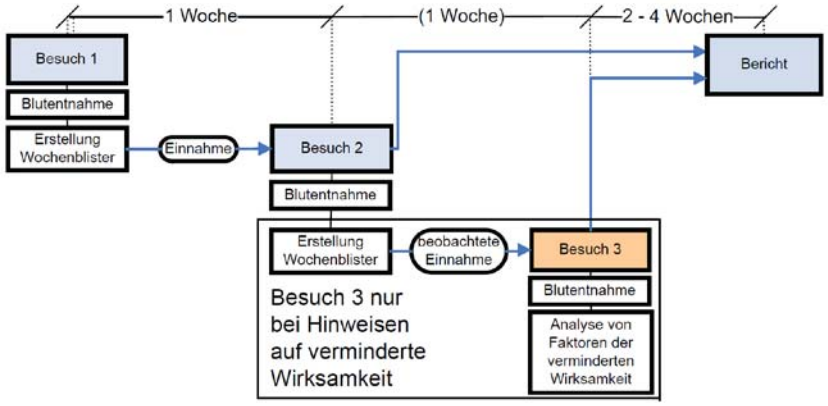
Warum wird diese Studie durchgeführt?
In den vergangenen Jahren wurden vermehrt Hinweise darauf gefunden, dass die Therapie mit Acetylsalicylsäure (z.B. Aspirin Cardio®) und Clopidogrel (Plavix®) nicht bei allen Patienten im gewünschten Ausmass wirksam ist. In neuerer Zeit werden deshalb Labortests angewendet, welche die verminderte Wirkung beim einzelnen Patienten festzustellen vermögen. Wir benützen erprobte Labortests, um herauszufinden, welche Patienten diesem Risiko ausgesetzt sind. Anschliessend werden wir analysieren, welche Faktoren bei diesen Patienten zu einer verminderten Wirkung beitragen. Die daraus gewonnenen Informationen können Ihrem Arzt / Ihrer Ärztin helfen, Massnahmen zur Optimierung der Arzneimitteltherapie zu treffen.

Das Ziel der Studie ist die Erkennung von Faktoren, die zu einer verminderten Wirksamkeit von Aspirin Cardio® bzw. dessen Generika sowie von Plavix® führen können. Die verminderte Wirksamkeit wird in der Fachliteratur auch als „Resistenz“ bezeichnet, wobei oft nicht genügend geklärt ist, in wie weit das Einnahmeverhalten der Patienten zu diesem Phänomen beiträgt. Nebst der Berücksichtigung anderer Faktoren wird deshalb in dieser Studie der Messung des Einnahmeverhaltens besondere Beachtung geschenkt. Dabei kommen verschiedene Techniken zur Anwendung. Zudem werden wiederholt Labortests durchgeführt, welche Anhaltspunkte zur Wirksamkeit der Therapie liefern können.

Bin ich zu einer Teilnahme verpflichtet?
Ihre Teilnahme an dieser Studie ist freiwillig. Wenn Sie auf die Teilnahme an dieser Studie verzichten, haben Sie keine Nachteile für Ihre weitere medizinische Betreuung zu erwarten. Das gleiche gilt, wenn Sie Ihre dazu gegebene Einwilligung zu einem späteren Zeitpunkt widerrufen. Diese Möglichkeit haben Sie jederzeit. Einen allfälligen Widerruf Ihrer Einwilligung bzw. den Rücktritt von der Studie müssen Sie nicht begründen. Im Falle eines Widerrufes werden die bis zu diesem Zeitpunkt erhobenen Daten weiter verwendet. Die im Rahmen der Studie erhobenen Blutproben werden nach Abschluss der Analyse vernichtet.

Was muss ich tun, wenn ich der Teilnahme zustimme?
Nach der Rekrutierung in der Arztpraxis werden Sie telefonisch durch das Studienzentrum am Med. Labor Olten kontaktiert. Die Studie dauert etwas mehr als eine Woche und umfasst zwei Besuche im Medizinischen Labor in Olten. Beim ersten Besuch werden wir sämtliche Medikamente, die Sie derzeit einnehmen müssen, in einen speziellen Wochenblister verpacken, eine Befragung zur Medikamenteneinnahme durchführen sowie eine venöse Blutprobe entnehmen. Während der anschliessenden Woche werden Sie die gewohnten Medikamente in der gleichen Dosierung wie bis anhin einnehmen. Am Ende der Woche werden wir erneut eine Blutprobe entnehmen. Aus den

beiden Blutproben zu Beginn und am Ende der Woche werden wir die Funktion der Blutplättchen messen und einige Routine-Labortests (Blutbild, Leber, Niere, Entzündungsparameter) durchführen.



Bei Hinweisen auf eine verminderte Wirksamkeit wird die Studie um eine weitere Woche fortgesetzt. Zum Ausschluss einer unvollständigen Einnahme muss in diesem Fall von Montag bis Freitag täglich eine Medikamentendosis unter Beobachtung in der Arztpraxis oder im Studienzentrum eingenommen werden. Erst danach ist eine Untersuchung auf andere Faktoren, die zu eine Verminderung der Medikamentenwirkung führen können, sinnvoll. Diese Analyse beinhaltet unter anderem genetische Tests. Diese können aus einer vorgängig entnommenen Blutprobe durchgeführt werden und erfordern keinen neuen Besuch im Studienzentrum.

Über Ihre Ergebnisse in der Studie werden Sie und Ihr Arzt durch einen gut verständlichen Bericht orientiert. Sollten Ihre Resultate Anlass dazu geben, Ihre Arzneimtteltherapie bezüglich der Blutplättchenfunktion zu optimieren, werden wir Ihnen eine ärztliche Konsultation empfehlen, oder Ihr Arzt wird Sie zu einer Besprechung im Rahmen einer normalen Konsultation kontaktieren.

Welche Vorteile hat die Studie für mich?

- Die Teilnahme an dieser klinischen Studie kann für Sie den direkten Nutzen haben, dass eine allfällige verminderte Wirksamkeit von Aspirin Cardio® (bzw. Generikum) oder Plavix® entdeckt werden könnte. Dadurch kann Ihr Arzt / Ihre Ärztin Massnahmen ergreifen, um diesem Zustand entgegen zu wirken (z.B. Wechsel auf andere Medikamente, andere Dosierung).
- Dank Ihrer Studienteilnahme können die Ergebnisse auch anderen Personen zugute kommen.

Welche Risiken und Unannehmlichkeiten sind mit der Teilnahme verbunden?

- Die Wirkungen und Nebenwirkungen unterscheiden sich durch die Studienteilnahme nicht, da keine Medikamente zur Anwendung kommen, die sie nicht schon verschrieben erhalten haben.
- Aufwand und Unannehmlichkeiten beschränken sich auf einen zweimaligen Besuch im Studienzentrum am Med. Labor Olten mit je einer venösen Blutentnahme. Bei der Blutentnahme kann unter Umständen Unwohlsein, Schwindelgefühl oder sogar Ohnmacht auftreten. An der Nadeleinstichstelle können Rötungen, Schmerzen, Schwellungen, blaue Flecken oder selten eine Infektion auftreten.
- In den Fällen mit Verdacht auf eine unzureichende Wirkung der Medikamente ist die Verlängerung der Studie um eine Woche notwendig, und die Medikamente müssen von Montag bis Freitag entweder in der Arztpraxis oder im Studienzentrum unter direkter Beobachtung eingenommen werden und ein dritter Besuch im Studienzentrum (inkl. Blutentnahme) ist notwendig.

Wer hat Zugang zu den Daten, und wie wird die Vertraulichkeit gewährleistet?

In dieser Studie werden persönliche Daten von Ihnen erfasst. Diese Daten werden anonymisiert. Sie sind nur Fachleuten zur wissenschaftlichen Auswertung zugänglich. Im Rahmen von Inspektionen können Mitglieder der zuständigen Behörden Einsicht in Ihre Originaldaten nehmen. Ebenso kann die zuständige Ethikkommission Einsicht in die Originaldaten nehmen. Während der ganzen Studie und

bei den erwähnten Kontrollen wird die Vertraulichkeit strikt gewahrt. Ihr Name wird in keiner Weise in Rapporten oder Publikationen, die aus der Studie hervorgehen, veröffentlicht.

Wer überwacht die Studie?
Diese Studie wird nach geltenden schweizerischen Gesetzen und nach international anerkannten Grundsätzen durchgeführt. Die Studienverfahren wurden von der Ethikkomission Aargau geprüft und genehmigt. Die Entscheide dieser Ethikkommission werden vom Kanton Solothurn anerkannt.

Welche für mich kostenlosen Leistungen werden während der Studie erbracht?
Die in dieser Patienteninformation erwähnten Laboruntersuchungen sowie die Methoden zur Messung des Einnahmeverhaltens und die Erstellung des Wochenblisters werden kostenlos durchgeführt. Auch die Analyse der Daten und die Erstellung des schriftlichen Berichtes zu Ihren Händen mit Kopie an Ihren Arzt / Ihre Ärztin bleibt sowohl für Sie als auch für Ihre Krankenkasse ohne Kostenfolge.

Für die Dauer der Studie kommen Ihre eigenen Medikamente zur Anwendung, welche Sie selbst bezahlt bzw. von Ihrer Krankenkasse rückvergütet erhalten haben. Konsultationen und Massnahmen, welche in Folge der von Ihnen erzielten Resultate geplant und durchgeführt werden, obliegen der Verantwortung Ihres behandelnden Arztes / Ihrer Ärztin und erfolgen im Rahmen einer gewöhnlichen Konsultation.

Werde ich für meine Teilnahme entschädigt?
Für die Teilnahme an dieser klinischen Studie ist keine finanzielle Entschädigung vorgesehen.

Gründe, welche ohne Ihre Zustimmung zu einem Studienabbruch führen können
Ihre Teilnahme kann durch den Prüfarzt abgebrochen werden, wenn finanzielle, personelle oder organisatorische Gründe eine Weiterführung der Studie verunmöglichen. Die bis dahin ermittelten Daten werden – sofern im medizinischen Sinne nützlich – dennoch Ihnen und Ihrem Arzt / Ihrer Ärztin zur Verfügung gestellt.

Wer haftet, wenn wegen der Studienteilnahme gesundheitliche Schäden entstehen?
Das Med. Labor Olten MLO AG ersetzt Ihnen Schäden, die Sie gegebenenfalls durch die Teilnahme an dem klinischen Versuch erleiden. Zu diesem Zweck wurde von der Betriebshaftpflichtversicherung des Med. Labor Olten MLO AG (Basler Versicherungen) eine ergänzende Versicherungsdeckung zu Ihren Gunsten schriftlich bestätigt.

An wen kann ich mich bei weiteren Fragen wenden?
Bei Unklarheiten, Notfällen, unerwarteten oder unerwünschten Ereignissen, die während der Studie oder nach deren Abschluss auftreten, können Sie sich jederzeit an eine der untenstehenden Kontaktpersonen wenden. Ihr erster Ansprechpartner ist Herr Philipp Walter am Studienzentrum.

Studienzentrum	**Prüfarzt**
Philipp Walter, dipl. pharm. Med. Labor Olten Frohheimweg 12 4603 Olten Tel. 062 205 60 36	Dr. med. Michel Romanens Ziegelfeldstrasse 1 4600 Olten Tel. 062 212 44 10

8.5. INFORMED CONSENT, PART I (GENERAL PRACTITIONER)

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Kontakt-aufnahme

Einverständniserklärung

für die Kontaktaufnahme durch das Studienzentrum

Wir möchten Ihnen die Gelegenheit zur Teilnahme an einer klinischen Studie bieten, die sich mit der verminderten Wirksamkeit von Aspirin Cardio® (und Generika) und Plavix® befasst. Damit wir Sie vom Studienzentrum telefonisch kontaktieren dürfen, benötigt die Arztpraxis Ihre Erlaubnis zur Weitergabe Ihres Namens und Ihrer Telefonnummer. Mit Ihrer Unterschrift erlauben Sie der Arztpraxis zudem, uns eine Liste der von Ihnen eingenommenen Medikamente zuzustellen.

Falls Sie damit einverstanden sind, bitten wir Sie, das vorliegende Dokument zu unterzeichnen. Die Med. Praxisassistentin wird Ihnen ein Couvert mit der Patient/-innen-Information aushändigen. Darin sind detaillierte Informationen zur Studie enthalten. Bitte lesen Sie diese Informationen sorgfältig durch. Herr Philipp WALTER vom Studienzentrum der Universität Basel wird sie innerhalb der nächsten zwei Wochen kontaktieren und Sie bezüglich der Teilnahme an der Studie anfragen sowie zur Klärung allfälliger Fragen zur Verfügung stehen.

Erst zum Zeitpunkt eines Besuchs am Studienzentrum wird Ihnen die Einverständniserklärung für die Studienteilnahme vorgelegt. Sollten Sie sich anlässlich des Telefongespräches oder beim ersten Besuch des Studienzentrums gegen eine Teilnahme an der Studie aussprechen, so werden die von der Arztpraxis an das Studienzentrum übermittelten Informationen umgehend vernichtet.

Titel der Studie:	Aspirin®- und Plavix®-Resistenz
	Olten (SO)
Prüfärztin/Prüfarzt Namen und Adressen:	Dr. med. M. Romanens, Ziegelfeldstrasse 1, 4600 Olten
Patientin/Patient NAME und Vorname: Geburtsdatum: Geschlecht:	.... / ..... / ..... (TT / MM / JJJJ) ☐ männlich ☐ weiblich

- Ich bin einverstanden, dass meine Adresse und Telefonnummer sowie eine Liste der von mir eingenommenen Medikamente von der Arztpraxis an das Studienzentrum weitergeleitet wird, damit dieses mich für die Anfrage zur Studienteilnahme kontaktieren kann.
- Ich bin unter den folgenden Telefonnummern erreichbar:

Geschäft: ..... ☐ vormittags ☐ nachmittags ☐ abends

Privat: ..... ☐ vormittags ☐ nachmittags ☐ abends

Mobiltelefon: ..... ☐ vormittags ☐ nachmittags ☐ abends

Ort, Datum	Unterschrift der Patientin/des Patienten

Bestätigung des Arztpraxis:

Ort, Datum	Praxisstempel und Unterschrift der Arztpraxis

Praxismitarbeiter: Bitte Liste der verordneten Medikamente auf der Rückseite ausfüllen!

Liste der verordneten Medikamente

Patient/-in	NAME, Vorname:	Jahrgang: .....

Anstelle dieser Liste kann ein Ausdruck aus der Praxissoftware oder eine andere aktuelle Auflistung der verordneten Medikamente mit Datum und Unterschrift dem Studienzentrum zugestellt werden.

1	**Medikament**					**Stärke**	☐g ☐mg ☐µg
	Dosierung	Zutreffende Dosierung bitte umkreisen (O) oder einzunehmende Dosierung > 2 notieren					
		morgens	mittags	abends	zur Nacht	bei Bedarf	
		½ 1 2 ...	½ 1 2 ...	½ 1 2 ...	½ 1 2 ...	½ 1 2 ...	
2	**Medikament**					**Stärke**	☐g ☐mg ☐µg
	Dosierung	Zutreffende Dosierung bitte umkreisen (O) oder einzunehmende Dosierung > 2 notieren					
		morgens	mittags	abends	zur Nacht	bei Bedarf	
		½ 1 2 ...	½ 1 2 ...	½ 1 2 ...	½ 1 2 ...	½ 1 2 ...	
3	**Medikament**					**Stärke**	☐g ☐mg ☐µg
	Dosierung	Zutreffende Dosierung bitte umkreisen (O) oder einzunehmende Dosierung > 2 notieren					
		morgens	mittags	abends	zur Nacht	bei Bedarf	
		½ 1 2 ...	½ 1 2 ...	½ 1 2 ...	½ 1 2 ...	½ 1 2 ...	
4	**Medikament**					**Stärke**	☐g ☐mg ☐µg
	Dosierung	Zutreffende Dosierung bitte umkreisen (O) oder einzunehmende Dosierung > 2 notieren					
		morgens	mittags	abends	zur Nacht	bei Bedarf	
		½ 1 2 ...	½ 1 2 ...	½ 1 2 ...	½ 1 2 ...	½ 1 2 ...	
5	**Medikament**					**Stärke**	☐g ☐mg ☐µg
	Dosierung	Zutreffende Dosierung bitte umkreisen (O) oder einzunehmende Dosierung > 2 notieren					
		morgens	mittags	abends	zur Nacht	bei Bedarf	
		½ 1 2 ...	½ 1 2 ...	½ 1 2 ...	½ 1 2 ...	½ 1 2 ...	
6	**Medikament**					**Stärke**	☐g ☐mg ☐µg
	Dosierung	Zutreffende Dosierung bitte umkreisen (O) oder einzunehmende Dosierung > 2 notieren					
		morgens	mittags	abends	zur Nacht	bei Bedarf	
		½ 1 2 ...	½ 1 2 ...	½ 1 2 ...	½ 1 2 ...	½ 1 2 ...	
7	**Medikament**					**Stärke**	☐g ☐mg ☐µg
	Dosierung	Zutreffende Dosierung bitte umkreisen (O) oder einzunehmende Dosierung > 2 notieren					
		morgens	mittags	abends	zur Nacht	bei Bedarf	
		½ 1 2 ...	½ 1 2 ...	½ 1 2 ...	½ 1 2 ...	½ 1 2 ...	
8	**Medikament**					**Stärke**	☐g ☐mg ☐µg
	Dosierung	Zutreffende Dosierung bitte umkreisen (O) oder einzunehmende Dosierung > 2 notieren					
		morgens	mittags	abends	zur Nacht	bei Bedarf	
		½ 1 2 ...	½ 1 2 ...	½ 1 2 ...	½ 1 2 ...	½ 1 2 ...	
9	**Medikament**					**Stärke**	☐g ☐mg ☐µg
	Dosierung	Zutreffende Dosierung bitte umkreisen (O) oder einzunehmende Dosierung > 2 notieren					
		morgens	mittags	abends	zur Nacht	bei Bedarf	
		½ 1 2 ...	½ 1 2 ...	½ 1 2 ...	½ 1 2 ...	½ 1 2 ...	
10	**Medikament**					**Stärke**	☐g ☐mg ☐µg
	Dosierung	Zutreffende Dosierung bitte umkreisen (O) oder einzunehmende Dosierung > 2 notieren					
		morgens	mittags	abends	zur Nacht	bei Bedarf	
		½ 1 2 ...	½ 1 2 ...	½ 1 2 ...	½ 1 2 ...	½ 1 2 ...	

Ort, Datum	Praxisstempel und Unterschrift der Arztpraxis

Version vom 15.09.09 2 / 2

8.6. INFORMED CONSENT, PART II (STUDY CENTRE)

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Studien-teilnahme

Einverständniserklärung zur Studienteilnahme

Titel der Studie:	**Aspirin®- und Plavix®-Resistenz**
Ort der Studie:	Olten (SO)
Prüfärztin/Prüfarzt Name und Adresse:	Dr. med. M. Romanens, Ziegelfeldstrasse 1, 4600 Olten
Patientin/Patient	
NAME und Vorname:	....
Geburtsdatum:	..... / ..... / ..... (TT / MM / JJJJ)
Geschlecht:	☐ männlich ☐ weiblich

- 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 03.07.09 gelesen und verstanden. Meine Fragen im Zusammenhang mit der Teilnahme an dieser Studie sind mir zufriedenstellend beantwortet worden. Ich kann die schriftliche Patienten-information 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.*

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Studien-teilnahme

Unabhängige Befragung

Im Zusammenhang mit der wissenschaftlichen Fragestellung, welche durch die vorliegende Studie zur Aspirin®- und Plavix®-Resistenz beforscht wird, befindet sich eine Folgestudie unserer Forschungsgruppe in Planung. Gerne würden wir Sie deshalb zu einem späteren Zeitpunkt anfragen, ob Sie zu einer erneuten Teilnahme bereit wären. 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

8.7. QUESTIONNAIRES FOR DATA COLLECTION

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UNI BASEL

QD-QA

Datenerhebungsformular für Arztpraxis

für die Studie zur Clopidogrel- und Aspirin-Resistenz

☞ Das Studienzentrum wird Ihnen mitteilen, welche Patienten aus Ihrer Praxis in die Studie aufgenommen werden konnten und welche Patienten Codes Ihren Patienten zugeteilt wurden. Füllen Sie bitte anschliessend das Formular sorgfältig aus und faxen Sie es an das Studienzentrum am Med. Labor Olten MLO (→ Herr Philipp WALTER; 062 205 60 39). Besten Dank!

1. Datum und Patientenidentifikation

Datum: ☐☐/☐☐/☐☐ (TT/MM/JJ)
Patienten Code: ☐☐ - ☐☐☐☐ Geschlecht: ☐männlich ☐weiblich

2. Thrombozytenaggregationshemmung

Therapie mit:
☐Aspirin Cardio® (oder ASS-Generikum) seit: ☐☐/☐☐/☐☐ (TT/MM/JJ)
☐Plavix® 75 mg seit ☐☐/☐☐/☐☐ (TT/MM/JJ) bis ☐☐/☐☐/☐☐ (TT/MM/JJ)

Indikation für die Therapie mit Acetylsalicylsäure (ASS) und/oder Plavix® (Clopidogrel):
☐Primärprävention
☐Sekundärprävention nach:
☐kardiovaskulärem Ereignis am: ☐☐/☐☐/☐☐ (TT/MM/JJ)
Diagnose: .....
und / oder
☐cerebrovaskulärem Ereignis am: ☐☐/☐☐/☐☐ (TT/MM/JJ)
Diagnose: .....
☐Status nach Koronararteriendilatation / Stent am: ☐☐/☐☐/☐☐ (TT/MM/JJ)
☐bare metal stent
oder ☐drug eluting stent
oder ☐kein stent
☐manifeste Re-Okklusion am: ☐☐/☐☐/☐☐ (TT/MM/JJ)
oder ☐wiederholte Komplikationen
oder ☐bisher keine Komplikationen

3. Andere Diagnosen

☐D. mellitus ☐Typ 1 / ☐Typ 2 → (insulinpflichtig ☐ja / ☐nein)
☐Fettstoffwechselstörung (z.B. Hypercholesterinämie)
☐Bluthochdruck
☐Schilddrüsenfunktionsstörung → (☐Überfunktion oder ☐Unterfunktion)
☐Chronische Niereninsuffizienz ☐Periphere arterielle Verschlusskrankheit (PAVK)

Fortsetzung andere Diagnosen

☐ .....

☐ .....

☐ .....

☐ .....

4. Unerwünschte Arzneimittelwirkungen

Bitte geben Sie an, wenn der Patient / die Patientin seit Beginn der Therapie mit Thrombozytenaggregationshemmern unerwünschte Arzneimittelwirkungen erlitten hat.

☐ Blutungen ☐ ☐

☐ Gastrointestinale Ulzerationen ☐ ☐

☐ Andere: .....

☐ .....

5. Bemerkungen und Ergänzungen

.....

.....

.....

.....

.....

.....

.....

6. Praxisstempel, Datum und Unterschrift

Datum: ☐☐/☐☐/☐☐ (TT/MM/JJ)

Praxisstempel
und Unterschrift:
.....

Allfällige Rückfragen sind zu richten an:

Herr / Frau ..... (❑ MPA / ❑ Arzt/Ärztin)

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QD-QP1

Patient/-innen Fragebogen zur Plavix® und Aspirin-Resistenz

Bitte beantworten Sie die folgenden Fragen wahrheitsgemäss und kreuzen Sie die richtigen Antworten. Fragen Sie bei allfälligen Unklarheiten nach. Besten Dank!

1. Datum ☐☐/☐☐/☐☐ (TT/MM/JJ) Patienten Code (TT/MM/JJ) (durch Studienmitarbeiter auszufüllen) ☐☐ - ☐☐☐☐

2. Fragen zur Person

Körpergewicht: ☐☐☐ kg Körpergrösse: ☐☐☐ cm

Falls Sie unsicher bezüglich diesen Angaben sind, ist eine Messung bei uns möglich.

3. Fragen zur sozioökonomischen Situation

Ich wohne:
- ☐ alleine
- ☐ zusammen mit Lebenspartner/-in
- ☐ mit meinen Kindern zusammen

Ich bin:
- ☐ voll berufstätig
- ☐ teilzeit berufstätig (Beschäftigungsgrad: ☐☐%)
- ☐ pensioniert oder beziehe eine Rente

4. Fragen zu Ihrer Schul- und Berufsausbildung (Mehrfachantwort möglich)

Ich habe:
- ☐ keinen Schulabschluss
- ☐ die obligatorische Schulzeit absolviert
- ☐ eine Berufslehre absolviert
- ☐ weiterführende Schulen absolviert (Handelsschule, Diplommittelschule, Kantonsschule)
- ☐ Universitäts- oder Fachhochschul-Abschluss

5. Fragen zum Gesundheitszustand und Gesundheitsverhalten

Meinen Gesundheitszustand schätze ich zur Zeit als:
- ☐ sehr gut
- ☐ eher gut
- ☐ eher schlecht
- ☐ schlecht

Ich bin:
- ☐ Nichtraucher(in) seit ☐☐/☐☐/☐☐ (TT/MM/JJ)
- ☐ Raucher(in) seit ☐☐/☐☐/☐☐ (TT/MM/JJ)
- ☐ rauche ☐☐ Zigaretten pro Tag *und / oder* ☐ rauche Pfeife

6. Fragebogen zum Medikamenten-Einnahmeverhalten

Bitte beantworten Sie nun auch den roten und den grünen Fragebogen.

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-QP2

Fragebogen zum Medikamenten-Einnahmeverhalten

MMAS-8: Morisky Medication Adherence Scale

Leute, die Medikamente einnehmen müssen, haben verschiedene Aspekte ihres Einnahmeverhaltens aufgedeckt und wir möchten gerne wissen, welche Erfahrungen Sie gemacht haben. Es gibt keine richtige oder falsche Antwort. Bitte beantworten Sie jede Frage nach Ihrer persönlichen Erfahrung in Bezug auf Ihre Medikamente.

	JA	NEIN
1. Vergessen Sie manchmal, Ihre Medikamente zu nehmen?	☐	☐
2. Manchmal wird ein Medikament nicht eingenommen, und zwar aus einem anderen Grund, als Vergesslichkeit. Wenn Sie an die letzten 2 Wochen denken, gab es Tage, an welchen Sie Ihre Medikamente nicht genommen haben?	☐	☐
3. Haben Sie jemals die Einnahme Ihrer Medikamente verringert oder gestoppt ohne Ihren Arzt/Ihre Ärztin zu informieren, weil Sie sich schlechter fühlten nach der Einnahme?	☐	☐
4. Wenn Sie reisen oder Ihr Zuhause verlassen, vergessen Sie manchmal Ihre Medikamente mitzunehmen?	☐	☐
5. Haben Sie Ihre Medikamente gestern genommen?	☐	☐
6. Wenn Sie das Gefühl haben, dass Ihre Krankheit unter Kontrolle ist, hören Sie manchmal mit der Einnahme Ihrer Medikamente auf?	☐	☐
7. Jeden Tag Medikamente zu nehmen empfinden viele Personen als lästig. Fühlen Sie sich manchmal schikaniert, wenn Sie den Therapieplan für Ihre Krankheit genauestens einhalten müssen?	☐	☐

8. Wie oft haben Sie Mühe, sich an die Einnahme aller Ihrer Medikamente zu erinnern?

Bitte kreuzen Sie eine der folgenden Antworten an.

Nie/selten	Hin und wieder	Manchmal	Fast immer	Immer
☐	☐	☐	☐	☐

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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.	☐	☐	☐	☐	☐

8.8. LOCAL ETHICS COMMITTEE APPROVAL

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

8.9. SWISSMEDIC NOTIFICATION

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).

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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

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CURRICULUM VITAE

Not available in the electronic version.