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Evaluation of oral anticoagulation therapy: rationale and design of the thrombEVAL study programme

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Abstract
Background: Since decades, oral anticoagulation (OAC) with vitamin K antagonists (VKA) is an established therapy for both prevention and treatment of thromboembolism in daily clinical routine. Increasing life expectancy, demographic changes, and novel oral anticoagulants have led to an increasing complexity of medical therapy. However, data on quality and management of VKA therapy with phenprocoumon in current medical care are limited. Our aim is to investigate the quality of OAC with VKA in current health care and to evaluate the potential for improvements.

Study design: The investigator-initiated thrombEVAL study programme comprises two cohorts of patients treated with vitamin K antagonists for oral anticoagulation therapy in real-life settings: a multicentre cohort of patients in regular medical care and a multilocal, single-centre cohort of patients in a telemedicine-based coagulation service. The study programme is expected to enrol a total number of approximately 2000 to 2500 patients. Both cohorts will build on a detailed clinical assessment of participants and anticoagulation therapy at study enrolment. Subsequently active and passive follow-up investigations are carried out to document and validate complications of the treatment. The primary short-term outcome is the distribution of time in therapeutic range; the primary long-term outcome comprises the composite of stroke, systemic embolism, myocardial infarction, major and clinically relevant bleeding, and death.

Conclusions: The thrombEVAL project will provide a large prospective observational cohort of patients predominantly treated with phenprocoumon. It will evaluate the quality of oral anticoagulation in regular medical care and a telemedicine-based coagulation service.

Keywords
Anticoagulants, coagulation service, vitamin K antagonist, phenprocoumon, quality of care, regular medical care, study design

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Introduction
Oral anticoagulant drugs are applied to prevent or treat thrombotic and thromboembolic events. The most frequent indications for oral anticoagulation treatment (OAC) comprise atrial fibrillation, venous thromboembolism, prosthetic heart valves, and peripheral vascular bypass surgery.¹⁻⁴ Increasing life expectancy and the demographic change will lead to a growing need for oral anticoagulation, as most diseases which require treatment such as atrial fibrillation – the most frequent indication – are more prevalent in the elderly.² The expanding complexity of haemostaseology results in high demands on the physician in charge: multimorbidity of older patients and the new diversity of options for OAC available by novel anticoagulant
drugs necessitate a careful consideration of benefits and risks of the treatment. The cost pressure on the healthcare system requires an economical use of medical resources. Major efforts are indispensable to provide further scientific evidence to cope with these clinical challenges.

For more than 60 years, vitamin K antagonists (VKAs) have been established as highly effective agents for OAC influencing the coagulation pathway. Therapy with VKAs requires individual adjustment of the dosage to keep the international normalized ratio (INR) within therapeutic range and to minimize anticoagulation-related side effects. The relationship between poor INR control and increased rates of stroke, bleeding, and death is well established. Many efforts have been undertaken to investigate this complex and multicausal issue and to identify predictors of stable INR adjustment.

Calculation of the time in therapeutic range (TTR) for the INR is an established surrogate marker to assess quality of OAC. TTR varies between physicians, clinical centres, and countries and was shown to be related with the outcome of the treatment. In randomized clinical trials, median TTR ranged from 58 to 67%. Data from general medical care suggest poorer anticoagulation control in the ‘real-life’ setting, with TTR ranging from 44 to 55%. Management of OAC by specialized anticoagulation clinics was reported to improve quality of VKA therapy and subsequently reduce anticoagulation-associated complications.

Worldwide, warfarin is the most commonly prescribed and most intensively investigated VKA in both clinical and observational trials. In Germany and other countries, however, phenprocoumon is predominantly administered for OAC. Current literature seems to support a class effect with regard to VKA and the quality of treatment. Nevertheless, VKAs show pharmacokinetic differences: phenprocoumon is a long-acting agent with a half-life time of approximately 5.5 days, whereas warfarin and acenocoumarol represent short-acting VKAs with an estimated half-life time of 36-42 h and 0.5-9 h, respectively. Data reporting about the quality of oral anticoagulation treatment with phenprocoumon in clinical trials and from clinical routine as well as data from the clinical implications of the pharmacokinetic variability of VKA are scarce.

New OAC inhibit directly activated coagulation factor X (e.g. rivaroxaban and apixaban) or thrombin (e.g. dabigatran) and have been recently investigated in clinical trials. The results indicate these drugs as promising alternatives to the established VKA therapy. Following their introduction into the health market for the first indications, current investigations focus on safety considerations, economic reasoning, and further therapeutic use (e.g. acute coronary syndrome) to expand their implementation in daily clinical care.

The thrombEVAL study programme has been initiated to evaluate treatment with VKAs (predominantly phenprocoumon) in the real-life setting of clinical care and its potential for optimization by a specialized telemedicine-based coagulation service (CS). ThrombEVAL represents the largest prospective multicentre study programme to comprehensively investigate OAC in the German healthcare system so far. The results of this project will help to accompany and support the development of optimized and individually tailored management and treatment concepts for patients requiring OAC.

**Objectives**

The primary objective of the thrombEVAL study programme is to assess the quality of anticoagulation therapy with VKA in the setting of RMC and in a specialized telemedicine-based CS and to compare both healthcare systems.

The secondary objectives of the thrombEVAL study programme are to: (i) assess determinants of anticoagulation control; (ii) investigate subgroups of patients with OAC (e.g. according to indication for treatment, concomitant diseases, and clinical status); (iii) explore the influence of sociodemographic or environmental factors and treatment characteristics (e.g. self-management of therapy, home visits); and (iv) examine mental health and quality of life under OAC. These aspects will be evaluated for their impact on risk stratification and analysed gender and age specifically, if possible. Lastly, health economics of the treatment and cost effectiveness of the specialized telemedicine-based CS will be evaluated.

**Outcome**

The primary outcome for quality of OAC varies with the time of analysis: The outcome in the short-term analysis is to analyse quality of OAC by the surrogate marker time in therapeutic range (TTR) for the international normalized ratio (INR). For mid-term interim analysis, the primary outcome is hospitalization. The primary long-term outcome is a net clinical benefit outcome, defined as the composite of stroke, systemic embolism, pulmonary embolism, myocardial infarction, major and clinically relevant nonmajor bleeding, and death.

Secondary outcome events for the mid- and long-term analysis are the individual components of the primary outcome (i.e. hospitalization, stroke, systemic embolism, pulmonary embolism, myocardial infarction, major bleeding, clinically relevant nonmajor
bleeding, death); in addition, minor bleeding, vascular causes of death, subtypes of stroke (haemorrhagic, ischaemic, nondisabling, fatal stroke), subtypes of bleeding (intracranial, extracranial), major adverse cardiac and cerebrovascular events, anticoagulation-associated hospitalization, stakeholder satisfaction and change in stakeholder satisfaction, mental illness, and comorbidities (see Supplementary Material, available online). Outcome events are defined in a charter for the assessment by the clinical event committee.

Study design

ThrombEVAL is an investigator-initiated, observational cohort study programme. It comprises two cohorts of patients with VKAs for oral anticoagulation therapy: a multicentre cohort including patients in regular medical care (RMC; i.e. outpatient treatment of oral anticoagulation either by general physicians, specialists, or outpatient clinics) and a single-centre cohort including patients being treated in a specialized CS. Both cohorts build on a detailed clinical assessment of participants for the study purposes at the time of study inclusion. In the cohort of RMC, anticoagulation control is recorded from the anticoagulation pass in the baseline examination; two follow-up visits are performed at year 1 and 2 by computer-assisted personal interviews to assess and validate the outcome. Study staff are in charge for documenting the clinical status only and do not interfere with the medical treatment of oral anticoagulation in RMC. In the CS, anticoagulation control and outcome is recorded constantly in an electronic patient file (for details, see the section on the coagulation service) for 2 years. Mortality will be assessed in both cohorts via queries from the governmental registry offices at year 3, 4, and 5. An overview on the study flow is given in Figure 1.

Study sample, in- and exclusion criteria and patient recruitment

The study base for the cohort of RMC is the federal state of Rhineland-Palatinate in western mid-Germany with approximately 4 million predominantly white inhabitants of European descent. The CS operates in Rhine-Hesse, an eastern region of Rhineland-
Palatinate with approximately 600,000 inhabitants. Both study samples comprise patients with VKAs for oral anticoagulation therapy. Patients were included if they were aged ≥18 years at study inclusion and written informed consent was obtained from the patient (or legal guardian, if appointed). The inclusion criteria for the cohort of patients receiving oral anticoagulation therapy in RMC were oral anticoagulation therapy with VKA for at least 4 months in RMC including patients with self-management of oral anticoagulation therapy. The inclusion criteria for the cohort of patients receiving oral anticoagulation therapy in the telemedicine-based CS cohort were indication for oral anticoagulation therapy with VKA for at least 3 months (both VKA-naive and VKA-experienced patients) at enrolment including patients with self-management of oral anticoagulation therapy. Exclusion criteria for both cohorts were contraindication to VKA treatment (e.g. pregnancy or known hypersensitivity to VKAs) and participation in other clinical trials.

No specifications or restrictions are made with regard to the concomitant medication. Study enrolment for the multicentre cohort of RMC is carried out at hospitals. Subjects meeting the criteria can be enrolled independent of the reason for hospitalization. The CS is operated as a single-centre cohort study with multilocality of all information relevant for dosing, such as clinical status and complications. An electronic patient file (EPF, commercially distributed by PortaVita) is the central interface for treatment in the CS. It is accessible for authorized persons (CS, patient, physicians involved in treatment) via a secure internet connection and contains all treatment-relevant information on the patient. The EPF bridges spatial and temporal distances between patients, CS, and other physicians in charge. Phenprocoumon and alternatively warfarin are administered as VKA and adjusted to the individually defined therapeutic range. At study enrolment, baseline information is recorded for each patient; with the regular visits for INR control, detailed, and up-to-date clinical information including complications of OAC are documented via standardized data acquisition and automated electronic transfer of INR values from the laboratory database into the EPF. A tool with a dosing algorithm is included in the EPF and supports the preparation of individually optimized dosing schemes and the scheduling of visits for each patient by the CS. Patients with self-management of OAC are included in the service as well; these individuals have access to their personal EPF and record INR values and dosing schemes themselves. In this setting, the CS exercises monitoring function and intervenes only if medically indicated or demanded by the patient. A detailed workflow of the CS is outlined in Figure 2.

**Baseline and follow-up examinations**

Upon inclusion, data are recorded by a clinical visit, from medical records and laboratory data. The assessment includes a detailed medical history, medication, specific characteristics of the anticoagulation treatment, history of anticoagulation-associated complications, allergies, sociodemographics, environmental factors and the need for nursing care. Moreover, a questionnaire-based interview on experiences and satisfaction with OAC (including instruments for depression, PHQ-2) is carried out and all data from the anticoagulation treatment pass (including date, INR values, and dosing schemes) are copied. In the CS, additional information is collected from patients with a more detailed assessment of the clinical status including e.g. mini-mental state examination at baseline, questionnaires on alcohol use (AUDIT), and quality of life under OAC (DASS) at month 3 and a repeated questionnaire-based interview on experiences and satisfaction with OAC at months 6 and 15. Follow-up investigations by computer-assisted telephone interview or as close out visit in the CS comprise medication and clinical characteristics, medical history, anticoagulation-specific complications, hospitalization, and mortality.

**Data acquisition and processing and quality control**

Data are obtained by multimodal assessment including electronic case report files in a web-based and a client-version (offline) of a remote data entry system, questionnaire-based and computer-assisted telephone interviews, laboratory databases, and data queries on governmental registry offices for mortality statistics. Study centres and the CS are equipped with laptops for mobile and bedside documentation. Study monitoring is carried out by an independent institution. Paper documents are digitalized via double data entry. INR values are recorded from the documentation available (i.e. anticoagulation pass, electronic patient file) and reviewed per patient by defined criteria. Quality of INR adjustment is assessed as time in therapeutic range by internationally accepted methods.
Time intervals with up-titration or discontinuation of the anticoagulant drug are excluded from TTR calculation. All data undergo quality control by a central data management unit and are checked for completeness and correctness by a predefined algorithm with plausibility criteria before analysis.

**Statistical analysis and power considerations**

The recruitment period in the cohort of RMC and the cohort of the CS is planned for 24 months. A sample size of approximately 2000–2500 participants is envisaged for the RMC and of approximately 750–1000 participants for the CS. Statistical analyses are of explorative nature and will be carried out as follows: after inclusion of approximately half of the estimated total sample size in both cohorts (T1), after completion of 1-year follow-up in half (T2) and all (T3) of the participants in both cohorts, after completion of 2-year follow-up in half (T4) and all (T5) of the participants in both cohorts and after completion of mortality statistics at years 3 (T6), 4 (T7), and 5 (T8).

The primary outcome varies for each time of analysis as defined in section ‘outcome’. A statistical power of 80% is the aim. For comparing TTR between healthcare services, using a Mann–Whitney U-test (two-sided, \( \alpha = 0.05 \)) and assuming 600 in the CS cohort and 1200 in the RMC cohort with a drop-out rate of 20% due to missing data would detect a difference in TTR between cohorts of 4.2%. For comparing hospitalization between healthcare services after 12 months, an event rate of 21%/patient-year is assumed according to literature.\(^{14}\) Sample sizes of 400 in the CS cohort and 800 in the RMC cohort and a drop-out rate of 20% would be sufficient to detect a relative risk reduction of approximately 35–37%. For comparing the net clinical benefit outcome (for definition, see the section on outcome) between healthcare services after 24 months, an event rate of 11%/patient-year is assumed based on present data from clinical trials.\(^{14,15}\) Sample sizes of 800 in the CS cohort and 1600 in the RMC cohort and a drop-out rate of 20% would be sufficient to detect a relative risk reduction of approximately 27% for this outcome. Assuming a sample size ratio between CS and RMC of 1:2, Supplementary Figure 1 displays the power to detect differences in TTR depending on the sample size and the relation between power and sample size for defined hazard ratios.

**Study implementation**

The thrombEVAL study programme is led by a steering committee of academic investigators. The multicentre...
cohort study of patients in RMC is conducted in 21 study centres at hospitals in the area of Rhineland-Palatinate, Germany. The CS is operated as single-centre cohort study by the University Medical Centre Mainz of the Johannes Gutenberg University of Mainz with 16 service bases. The study monitoring is carried out by the Interdisciplinary Centre for Clinical Studies (IZKS), Mainz, Germany. A list of all academic persons involved in the conduct of the study is presented in the Acknowledgements. Approval of the local ethics committees (reference no. 837.407.10.7415/7416) and data safety commissioner was obtained at all sites before study initiation. All individuals are asked for informed written consent prior to study enrolment. The trial is registered at http://clinicaltrials.gov with the unique identifier NCT01809015.

Conclusions
The thrombEVAL study programme will generate the largest prospective, observational cohort treated predominantly with phenprocoumon and a detailed investigation of quality of oral anticoagulation therapy in the German healthcare system. The expected enrolment of a sample with approximately 2000 individuals will enable us to analyse the determinants in the real-world setting. There is an unmet clinical need for these data because results from clinical trials can be translated into daily clinical routine only to a limited extent. However, translation to cohorts with varying ethnicity should be done with caution. Supplementary to the data of well-investigated warfarin, the study programme with data on phenprocoumon will facilitate to compare VKAs with regard to quality of treatment. It will add information on the potential for optimization of oral anticoagulation treatment by a telemedicine-based CS including data on cost-effectiveness. Lastly, it will help to evaluate and accompany the implementation of new oral anticoagulants in daily clinical routine by extending the knowledge on current VKA therapy.

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The thrombEVAL study organization
The thrombEVAL study organization constitutes the thrombEVAL Study Group, which consists of the following:

Steering committee
Philipp S Wild (principal investigator); Thomas Münzel (coprincipal investigator), Manfred E. Beutel, Christine Espinola-Klein, Stavros Konstantinides, Karl Lackner, Helmut Schinzel (all Mainz, Germany).

Clinical event committee
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Data safety and monitoring board
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Clinical Trial Registration
This trial is registered at www.clinicaltrials.gov (unique identifier NCT01809015).

References


