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Centrum für Thrombose und Hämostase (CTH)

der Universitätsmedizin der Johannes Gutenberg- Universität Mainz

Oral anticoagulation therapy

– Clinical application and pleiotropic effects on the cardiovascular system

Therapie mit oralen Antikoagulanzien

– Klinische Anwendung und pleiotrope Effekte auf das kardiovaskuläre System

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TABLE OF CONTENTS

GLOSSARY OF ABBREVIATIONS

AF	Atrial fibrillation
Apo	Apolipoprotein
ATC	Anatomical therapeutic chemical
BMI	Body mass index
CCI	Charlson comorbidity index
CI	Confidence interval
CRP	C-reactive protein
CVD	Cardiovascular disease
DOAC	Direct oral anticoagulants
eGFR	Estimated glomerular filtration rate
F	Factor
IQR	Interquartile range
Gas-6	Growth arrest-specific gene 6
GHS	Gutenberg Health Study
HR	Hazard ratio
INR	International Normalized Ratio
LV	Left ventricular
MGP	Matrix Gla Protein
OAC	Oral anticoagulation
PAR	Protease-activated receptor
RR	Rate ratio
SNP	Single Nucleotide Polymorphism
TTR	Time in therapeutic range
VKA	Vitamin K -Antagonist

ORIGINAL ARTICLES

I. **Eggebrecht L**, Prochaska JH, Schulz A, Arnold N, Jünger C, Göbel S, Laubert-Reh D, Binder H, Beutel ME, Pfeiffer N, Blankenberg S, Lackner KJ, Spronk HM, Ten Cate H, Münzel T, Wild PS. Intake of vitamin k antagonists and worsening of cardiac and vascular disease: Results from the population-based Gutenberg Health Study. Journal of the American Heart Association. 2018;7(17):e008650.
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II. **Eggebrecht L**, Prochaska JH, Tröbs SO, Schwuchow-Thonke S, Göbel S, Diestelmeier S, Schulz A, Arnold N, Panova-Noeva M, Koeck T, Rapp S, Gori T, Lackner KJ, Ten Cate H, Münzel T, Wild PS. Direct oral anticoagulants and vitamin K antagonists are linked to differential profiles of cardiac function and lipid metabolism. Clinical Research in Cardiology. 2019 Jan 2 [Epub ahead of print]
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III. **Eggebrecht L**, Prochaska JH, Schleuter L, Nagler M, Hardt R, Schinzel H, Münzel T, Wild PS. [Physicians' opinion on health care in oral anticoagulation]. Deutsche Medizinische Wochenschrift. 2018;143:e76-e84.
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IV. **Eggebrecht L**, Nagler M, Göbel S, Lamparter H, Keller K, Wagner B, Panova-Noeva M, Ten Cate V, Bickel C, Lauterbach M, Espinola-Klein C, Hardt R, Münzel T, Prochaska JH, Wild PS. Relevance of Polypharmacy for Clinical Outcome in Patients Receiving Vitamin K Antagonists. Journal of the American Geriatric Society. 2019;67(3):463-70.
Impact factor$_{2017}$: 4.155; Grading for Publication$_{2017}$: A

SUMMARY IN ENGLISH

This dissertation highlights new aspects in the field of oral anticoagulation. Firstly, the influence of the long established vitamin K antagonists (VKA) and the alternative direct oral anticoagulants (DOAC) on subclinical parameters of cardiovascular disease was investigated. Furthermore, the work provides new findings in the field of health care research and considers high-risk groups for reduced therapeutic quality and clinical outcome.

Oral anticoagulants are prescribed for primary and secondary prevention of thromboembolic diseases. Main indications are atrial fibrillation, venous thromboembolism (i.e., pulmonary embolism, deep vein thrombosis) and mechanical heart valves. With the introduction of DOAC in 2008, alternatives to the established VKA became available. Since not only coagulation factors but also other proteins are targets of VKA and DOAC, anticoagulation therapy might exert pleiotropic effects. Investigations in this thesis have demonstrated that oral anticoagulation therapy affects the development and course of subclinical parameters of cardiovascular disease differentially. It was shown for the first time that VKA therapy had a negative impact on arterial stiffness, vascular morphology, cardiac structure and function, and inflammation. In contrast, DOAC are linked to improved cardiac function and lipid metabolism. These results strengthen the notion that oral anticoagulants have an impact on the development and progression of cardiovascular disease, which, however, notably depends on the substance. These potential effects on the cardiovascular system underline the challenging situation regarding high quality oral anticoagulation therapy. In addition, clinical factors such as polypharmacy among elderly patients with atrial fibrillation contribute to the difficulty of obtaining high quality anticoagulation therapy at lowest risk of adverse events. Patients with polypharmacy have an increased risk of complications and adverse events, so it is believed that they need particular monitoring (e.g., regular control of kidney function and dose testing) to avoid over- and under-dosing. The present results are of high clinical relevance, as a combination of both, treatment quality and clinical phenotype, are important aspects for the development of individualized anticoagulation therapy.

Specialized care could facilitate optimal personalized care in both VKA and DOAC treated patients as well as in high-risk patient groups.

SUMMARY IN GERMAN

Die vorliegende Dissertation zeigt neue Aspekte der Antikoagulationstherapie auf. Zunächst wurde der Einfluss der lang etablierten Vitamin K-Antagonisten (VKA) und der alternativen direkten oralen Antikoagulanzien (DOAK) auf subklinische Parameter der kardiovaskulären Erkrankung untersucht. Weiterhin liefert die Arbeit neue Erkenntnisse im Bereich Versorgungsforschung und betrachtet Risikogruppen für reduzierte Therapiequalität und deren klinischem Outcome.

Orale Antikoagulanzien werden zur Primär- und Sekundärprävention thromboembolischer Erkrankungen eingesetzt. Eine Indikation besteht vorwiegend bei Vorhofflimmern, venösen Thromboembolien (Lungenembolie und tiefe Venenthrombose) und nach Herzklappenersatz. Mit der Einführung von DOAK im Jahr 2008 stehen Alternativen zu den klassischen VKA zur Verfügung. Da nicht nur Gerinnungsfaktoren, sondern auch andere Proteine Angriffspunkte der VKA und DOAK sind, können orale Antikoagulanzien pleiotrope Effekte vermitteln. Die Arbeit legte näher, dass orale Antikoagulanzien die Entwicklung und den Verlauf (sub)klinischer kardiovaskulärer Erkrankungen unterschiedlich beeinflusst. Zum ersten Mal wurde gezeigt, dass die VKA-Therapie im negativen Zusammenhang mit arterieller Steifigkeit, Gefäßmorphologie, Herzstruktur- und funktion sowie Inflammation steht. Im Gegensatz hierzu sind DOAK mit einer verbesserten Herzfunktion und besseren Fettstoffwechsel assoziiert. Diese Ergebnisse verstärkt die Annahme, dass orale Antikoagulanzien einen Einfluss auf die Entwicklung und das Fortschreiten kardiovaskulärer Erkrankungen haben, die jedoch insbesondere abhängig von der Art der Substanz sind. Diese Ergebnisse unterstreichen das anspruchsvolle Ziel einer qualitativ hochwertigen Antikoagulationstherapie. Darüber hinaus tragen klinische Faktoren wie Polypharmazie bei älteren Patienten mit Vorhofflimmern zu der Schwierigkeit bei, eine qualitativ hochwertige Antikoagulationstherapie mit dem geringsten Risiko unerwünschte Ereignisse zu

erzielen. Patienten mit Polypharmazie zeigten ein erhöhtes Risiko für Komplikationen und negative Ereignisse. Daher lässt sich annehmen, dass diese Patientengruppe eine besondere Überwachung benötigt (z. B. regelmäßige Kontrolle der Nierenfunktion und Medikation), um Über- und Unterdosierungen zu vermeiden. Die vorliegenden Ergebnisse sind von hoher klinischer Relevanz, da die Kombination aus Behandlungsqualität und dem klinischen Phänotyp einen wichtigen Aspekt in der individualisierten Antikoagulationstherapie darstellt. Eine spezialisierte Versorgungsform könnte eine optimale personalisierte Versorgung sowohl von VKA- und DOAK-Patienten als auch Hochrisikogruppen ermöglichen.

GENERAL INTRODUCTION

Oral anticoagulation therapy is used for prevention and treatment of venous thrombosis and prevention of stroke associated with atrial fibrillation, mechanical heart valves and peripheral vascular surgery (1). Vitamin K antagonists (VKA) have been used for many decades for oral anticoagulation therapy. These compounds act by inhibiting the enzyme vitamin K-epoxide reductase (VKOR) involved in hepatic synthesis of the vitamin K-dependent plasma coagulation factors (F) II, VII, IX, and X, as well as the natural anticoagulants protein C and protein S (2). In 2008 direct oral anticoagulants (DOAC; formerly 'novel' oral anticoagulants) became available. They specifically inhibit factor IIa (dabigatran etexilate) or factor Xa (rivaroxaban, apixaban, edoxaban) (3, 4). DOAC offer potential advantages over VKA, such as rapid onset and offset of action, fewer drug and food interactions and a predictable anticoagulant effect that obviates the need for routine coagulation monitoring. The introduction of DOAC caused a paradigm shift in antithrombotic therapy, as clinical practice guidelines on antithrombotic therapy and prevention of thrombosis now express a preference for DOAC over VKA for patients with non-valvular atrial fibrillation, especially if newly initiated (5, 6).

In addition to the hemostatic effects of oral anticoagulants through interference with the coagulation system, previous experimental and clinical studies have indicated the potential for differential non-canonical effects of anticoagulants (7). It has been demonstrated that VKA result in a decreased activity of the vitamin K–dependent proteins matrix GIa protein (MGP) and growth arrest–specific gene 6 (Gas-6) by inhibiting the γ-carboxylation process (8). The deficiency of active MGP and Gas-6 provokes cell death, decreased contractility of vascular smooth muscle cells, and accelerated vascular calcification (9, 10). First pre-clinical investigations showed that VKA treatment resulted in medial vascular calcification (11), which was followed by the evaluation of VKA on vascular and valvular calcification in a clinical setting (12-

18). In contrast, accumulating evidence suggests that thrombin and FXa are important modulators in cellular mechanisms through the activation of protease-activated receptor (PAR)-mediated signaling (19). A total of four PARs (PAR1, PAR2, PAR3, and PAR4) have been identified, and their expression has been shown on a variety of cells (e.g., platelets, vascular smooth muscle cells, endothelial cells, fibroblasts, and leukocytes), which are involved in the pathophysiology of atherosclerosis and cardiovascular disease (20). In mice, inhibition of FXa and thrombin revealed inhibitory effects on the development of atherosclerosis compounded by the stabilization of atherosclerotic plaques through inhibition of lipid deposition and decreased atherogenesis and inflammation (21-27). Associations between the administration of the FXa-inhibitor rivaroxaban and improved cardiac function have also been shown in experimental studies (28, 29). Given the important role of vascular calcification and atherosclerosis in the pathophysiology of vascular stiffness and the correlation with increased inflammation and incident cardiovascular disease, oral anticoagulants may exert clinically relevant non-coagulant effects (30). To date, the clinical translation from experimental animal models to man regarding possible pleiotropic effects of anticoagulation therapy has not been implemented, but is urgently needed.

The introduction of DOAC in addition to the established VKA, has not only raised new questions with regard to additional effects beyond anticoagulation, but also increased the complexity of treatment options for the physician in charge. Several studies have indicated that quality of anticoagulation therapy and subsequent clinical outcome depends on the physician´s treatment, patient education, and are better if patients are followed in a specialized anticoagulation management system (31-33). Oral anticoagulation therapy always presents a trade-off between efficacy (i.e., thromboprophylaxis and thrombus resolution) and safety (i.e., risk of bleeding) leaving the physicians with challenges in daily clinical practice. Therefore, it is of great interest to assess the current perception of physicians regarding oral anticoagulation therapy, and evaluate possibly still unknown management oversights leading to reduced treatment quality and worse clinical outcome. One high-risk group which requires particular monitoring are elderly, multimorbid patients on multiple medications, a condition known as polypharmacy (34-36). The prevalence of polypharmacy in subjects with atrial fibrillation is high ranging from 40 to 95 percent (37, 38). It was shown that polypharmacy among VKA users is associated with higher risk of adverse drug reactions, poor adherence to

medical treatment, higher frequency of hospitalizations, bleeding and all-cause mortality (39, 40). Although the mechanism of possible drug interactions and clinical outcome in patients receiving short-acting anticoagulants like warfarin is established, evidence on the relevance for the clinical outcome of anticoagulated patients on long-acting phenprocoumon, the by far most commonly prescribed VKA in Germany, and polypharmacy is currently limited and might vary from recent reports on warfarin.

There is a growing need for better understanding non-canonical effects of anticoagulants to develop the concept of an individualized anticoagulation therapy. The current thesis aimed at comparing effects of both direct and indirect oral anticoagulant regimes on intermediate phenotypes of cardiovascular structure and functions in humans, and put the results into context of the development and progression of atherosclerosis and cardiovascular disease. Furthermore, it was deemed of great importance to evaluate the impact of polypharmacy on the quality of anticoagulation therapy and subsequent clinical outcome in patients receiving the VKA phenprocoumon. The findings of this latter study may be useful for the optimization of the management of VKA therapy in the high-risk situation of polypharmacy.

Intake of vitamin K antagonists and worsening of cardiac and vascular disease: Results from the population-based Gutenberg Health Study

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ORIGINAL RESEARCH

Intake of Vitamin K Antagonists and Worsening of Cardiac and Vascular Disease: Results From the Population-Based Gutenberg Health Study

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***Background*—**Preclinical data have indicated a link between use of vitamin K antagonists (VKA) and detrimental effects on vascular structure and function. The objective of the present study was to determine the relationship between VKA intake and different phenotypes of subclinical cardiovascular disease in the population.

***Methods and Results*—**Clinical and laboratory data, as well as medical–technical examinations were assessed from 15 010 individuals aged 35 to 74 years during a highly standardized 5-hour visit at the study center of the population-based Gutenberg Health Study. In total, the study sample comprised 287 VKA users and 14 564 VKA nonusers. Multivariable analysis revealed an independent association between VKA intake and stiffness index (β=+2.54 m/s; [0.41/4.66]; P=0.019), ankle-brachial index (β=−0.03; [−0.04/−0.01]; P<0.0001), intima-media thickness (β=+0.03 mm [0.01/0.05]; P=0.0098), left ventricular ejection fraction (β=−4.02% [−4.70/−3.33]; P<0.0001), E/E′ (β=+0.04 [0.01/0.08]; P=0.014) left ventricular mass (β=+5.34 g/m$^{2.7}$ [4.26/6.44]; P<0.0001), and humoral markers of cardiac function and inflammation (midregional pro-atrial natriuretic peptide: β=+0.58 pmol/L [0.50/0.65]; P<0.0001; midregional pro-adrenomedullin: β=+0.18 nmol/L [0.14/0.22]; P<0.0001; N-terminal pro B-type natriuretic peptide: β=+1.90 pg/mL [1.63/2.17]; P<0.0001; fibrinogen: β=+143 mg/dL [132/153]; P<0.0001; C-reactive protein: β=+0.31 mg/L [0.20/0.43]; P<0.0001). Sensitivity analysis in the subsample of participants with atrial fibrillation stratified by intake of VKA demonstrated consistent and robust results. Genetic variants in *CYP2C9*, *CYP4F2*, and *VKORC1* were modulating effects of VKA on subclinical markers of cardiovascular disease.

***Conclusions*—**These data demonstrate negative effects of VKA on vascular and cardiac phenotypes of subclinical cardiovascular disease, indicating a possible influence on long-term disease development. These findings may be clinically relevant for the provision of individually tailored antithrombotic therapy. **(*J Am Heart Assoc*. 2018;7:e008650. DOI: 10.1161/JAHA.118.008650.)**

Key Words: cardiovascular disease • oral anticoagulation • pharmacogenomic variants • vitamin K antagonists

Vitamin K antagonists (VKA) are recommended to patients with an indication for oral anticoagulation therapy to prevent thromboembolic complications.[1] Recent data imply that the intake of VKA involves effects beyond the well-known inhibition of the vitamin K–dependent coagulation factors (F) II, VII, IX, and X.[2] Experimental data suggest that VKA may

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Accompanying Data S1 and Tables S1 through S8 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.008650

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Clinical Perspective

What Is New?

- Detrimental effects of vitamin K antagonists on vascular and cardiac phenotypes of subclinical cardiovascular disease were observed in a large population-based cohort.
- The analysis demonstrated a relationship of vitamin K antagonists treatment with increased arterial stiffness, higher left ventricular mass, and decreased cardiac systolic function independent of the concomitant clinical profile.

What Are the Clinical Implications?

- Noncanonical effects of vitamin K antagonists merit critical consideration against the background of frequently coprevalent atherosclerosis and cardiovascular disease and may be relevant for the long-term management of patients with oral anticoagulation.
- Evaluating the findings in contrast to the treatment with direct-acting oral anticoagulants will be crucial to develop clinical implications for an individualized anticoagulation therapy.

decrease the activity of the vitamin K–dependent proteins matrix Gla protein (MGP) and growth arrest–specific gene 6 (Gas-6) by inhibiting the γ-carboxylation process.[3] Unlike coagulation factors, which are synthesized and carboxylated within the liver, MGP and Gas-6 are carboxylated within the vasculature.[4] Increased levels of undercarboxylated MGP have been associated with vascular calcification.[5] The deficiency of active MGP and Gas-6 provokes cell death, decreased contractility of vascular smooth muscle cells, and accelerated vascular calcification.[4,6] Studies have also demonstrated that VKA therapy is associated with vascular calcification.[7,8] Given the important role of vascular calcification in the pathophysiology of vascular stiffness and the correlation of calcification with increased serum levels of inflammatory markers, hypertension, and incident cardiovascular disease (CVD), VKA may exert clinically relevant noncoagulant effects.[9]

Since alternatives to VKA therapy are available for most indications, noncoagulant effects of VKAs on the development and progression of atherosclerosis and CVD may have clinically relevant implications.

Against this background, the present study investigated the interrelation between the intake of VKA and the progress and development of CVD in the setting of a large population-based cohort study.

Methods

The analysis presents clinical data of a large-scale population-based cohort with ongoing follow-up examinations. This project constitutes a major scientific effort with high methodological standards and detailed guidelines for analysis and publication to ensure scientific analyses on highest level. Therefore, data are not made available for the scientific community outside the established and controlled workflows and algorithms. To meet the general idea of verification and reproducibility of scientific findings, we offer access to data at the local database in accordance with the ethics vote upon request at any time. The GHS (Gutenberg Health Study) steering committee, which comprises a member of each involved department and the head of the GHS, convenes once a month. The steering committee decides on internal and external access of researchers and use of the data and biomaterials based on a research proposal to be supplied by the researcher. Interested researchers make their requests to the head of the GHS (Philipp S. Wild; philipp.wild@unimedizin-mainz.de).

Study Sample

We investigated data of 15 010 individuals (age range 35–74 years) enrolled in the GHS, a population-representative, prospective, observational, single-center cohort study in the Rhine-Main region in Midwestern Germany. Participants were enrolled between April 2007 and April 2012 and underwent a detailed 5-hour medical–technical examination in the study center. The sample was drawn randomly from the local registration offices with equal strata for sex, residence (urban and rural), and age decades. Details of the study design have been published elsewhere.[10] The study complies with the principles outlined in the Declaration of Helsinki. The study protocol, study documents, and sampling design were approved by the Ethics Committee of the State Chamber of Physicians of Rhineland-Palatinate, Germany (reference number 837.020.07 (5555)) and by local institutional review boards. All study participants provided written informed consent.

Data Assessment

For the current analysis, information was obtained during the baseline visit at the study center. All study participants underwent comprehensive cardiovascular phenotyping at the study platform (see Data S1 for a detailed description of definitions for traditional cardiovascular risk factors and comorbidities used in the present analysis). Current medication use including medication on demand was recorded digitally by scanning the drug identification bar code from drug packages or alternatively established on the basis of self-reported information from participants (eg prescription plan). History of drug intake and the type of prescription (self-medication versus prescription by a physician) were recorded for the medication. Central pharmaceutical numbers were translated into the Anatomical Therapeutic Chemical code of the current

pharmaceutical index. Individuals with regular or current VKA use (Anatomical Therapeutic Chemical Code: B01AA) were defined as users and nonusers as the reference group.

Laboratory Analyses

Routine laboratory parameters (ie blood glucose, creatinine, lipids, fibrinogen, and blood count) were measured using standardized methods from fresh venous blood samples in all 15 010 study participants at enrollment in the central laboratory of the University Medical Center. For biobanking, samples were aliquoted and stored at −80°C immediately after blood draw. Specific biomarkers were analyzed in the subsample of the first 5000 participants: midregional pro-atrial natriuretic peptide (BRAHMS AG), midregional pro-adrenomedullin (BRAHMS AG), N-terminal pro B-type natriuretic peptide (Roche Diagnostics), high-sensitivity (hs) D-dimer (Instrumentation Laboratory), thrombomodulin (Sekisui Diagnostics), high-sensitivity C-reactive protein (hs-CRP) (Abbott), IL-18 (MBL), IL-1 receptor antagonist (R&D Systems), and myeloperoxidase (Prognostix) levels were measured using commercially available assays according to the manufacturer's recommendation. FII, FVII, FVIII, FIX, FX, FXI, tissue factor, and von Willebrand factor measurements were performed on a Siemens BCS-XP device. Collection, processing, handling, and storage of blood specimens were performed according to specific standard operating procedures.

Single Nucleotide Polymorphisms for VKA Metabolism

Single selected single nucleotide polymorphisms (SNPs) in the presently available genetic variant data set were used for this analysis. Detailed description of SNP selection is given in the Supplemental Material. Genetic information was available from 4175 of the first 5000 subjects enrolled. Genome-wide genotyping was performed using Affymetrix Genome-Wide Human SNP array 6.0 (Affymetrix, Santa Clara, CA), which assays 925.939 SNPs. SNPs contributing to the dose variability of vitamin K antagonists were selected from the genome-wide association studies catalogue (https://www.ebi.ac.uk/gwas/) maintained by the National Human Genome Research Institute using the following search terms: "warfarin," "phenprocoumon," "anticoagulants," and "vitamin K antagonist".

Data Management and Statistical Analysis

A central data management unit was in charge of quality control including the performance of plausibility tests and review for completeness by predefined algorithms. Descriptive statistics were generated for all variables. For comparisons of binary and continuous variables, prevalence ratios and relative differences were calculated, respectively. In linear regression models, surrogate parameters of clinical and subclinical CVD were related to VKA treatment. Skewness was evaluated by density plot and log-transformed where appropriate. Covariates were selected on the basis of known cardiovascular risk factors and significant findings from the univariate analysis. Linear regression models were used to screen for interaction by including the interaction terms age×VKA and sex (women)×VKA in the model. Since antihypertensive drugs and statins are known to influence cardiovascular function and structure, multivariable linear models were adjusted accordingly. To evaluate a potential time-dependent effect of VKA use on surrogate markers of CVD, VKA treatment was stratified according to treatment length with a cutoff point of 3 years. To investigate a homogeneous subsample of VKA users, a subgroup analysis was conducted in the individuals diagnosed with atrial fibrillation and a CHA_2DS_2-VASc score of ≥ 1 (as such an indication for treatment with oral anticoagulation). Inverse probability of treatment weighting using the propensity score was performed in individuals with diagnosed atrial fibrillation/venous thromboembolism only under consideration of the cardiovascular profile (ie presence of traditional cardiovascular risk factors and history of cardiovascular diseases). Multivariable regression models with surrogate markers of CVD as dependent variables were conducted to investigate their relationship with SNPs encoding genes involved in the metabolism of VKA (as independent variable). Because of the explorative character of the analysis, a significance threshold was not defined for *P* values. *P* values were interpreted as continuous measure of statistical evidence. Statistical data analyses were conducted using the software program R, version 3.3.1 (http://www.r-project.org).

Results

Comparisons of Clinical and Biochemical Characteristics According to VKA Intake

Of 15 010 study participants, 287 (1.9%) received VKA (282 phenprocoumon and 5 warfarin) at the time of examination. A total of 159 subjects were excluded from the analysis (156 individuals with missing information on medication intake and 3 individuals receiving novel, direct-acting anticoagulants), resulting in a sample size of 14 851 individuals for the present analysis. Table 1 displays cardiovascular risk factors and comorbidities according to VKA use. Subjects with current VKA use were about 12 years older and more likely to be male. As expected, VKA users had a higher cardiovascular burden. The strongest inequalities in prevalence were seen for the entities with indication for treatment with oral anticoagulation, atrial fibrillation, and pulmonary embolism. The

Table 1. Cardiovascular Risk Profile of the Study Sample According to VKA Intake

	No Intake of VKA (N=14 564)	Intake of VKA (N=287)
Age, y	55.0 (46.0/64.0)	67.0 (61.0/71.0)
Sex (female), % (n)	50.0 (7282)	30.3 (87)
Traditional cardiovascular risk factors, % (n)		
Diabetes mellitus	7.4 (1069)	18.2 (52)
Dyslipidemia	29.3 (4257)	42.7 (122)
Family history of myocardial infarction and/or stroke	22.1 (3221)	24.0 (69)
Hypertension	49.5 (7208)	72.5 (208)
Obesity	25.0 (3638)	41.6 (119)
Smoking	19.5 (2834)	14.8 (42)
Comorbidities, % (n)		
Atrial fibrillation	2.2 (315)	58.1 (161)
Cancer	9.0 (1305)	16.8 (48)
Chronic kidney disease	3.1 (450)	14.7 (42)
Chronic obstructive pulmonary disease	5.0 (721)	8.7 (25)
Congestive heart failure	1.1 (158)	14.0 (40)
Coronary artery disease	4.1 (582)	21.3 (58)
Deep vein thrombosis	3.4 (498)	28.6 (80)
Liver disease	0.7 (107)	1.0 (3)
Myocardial infarction	2.7 (394)	15.7 (44)
Peripheral artery disease	3.1 (448)	18.4 (52)
Peripheral vascular bypass surgery	0.2 (31)	6.3 (18)
Pulmonary embolism	0.1 (13)	4.5 (13)
Stroke	1.6 (238)	14.4 (40)

Data are expressed as the relative and absolute frequencies for binary variables, for continuous variables as median with 25th/75th percentiles. Information on medication-based Anatomical Therapeutic Chemical code was available for 14 851 individuals. A total of 3 individuals received direct-acting anticoagulants and were therefore excluded from the analysis. VKA indicates vitamin K antagonists.

smallest differences were observed for current smoking and family history of myocardial infarction or stroke. With regard to indication for oral anticoagulation therapy, the majority of study participants (58.1%) had atrial fibrillation, followed by venous thromboembolism (33.1%). Subjects with oral anticoagulation were more likely to be using antidiabetic medications, antihypertensive drugs, diuretics, and lipid-modifying drugs. The intake of antiplatelet drugs did not differ between both groups (9.1% and 10.3% for VKA users and nonusers, respectively; Table S1).

Surrogate markers of clinical and subclinical CVD according to VKA intake are summarized in Table 2. As expected from the clinical characteristics, subjects with VKA treatment had a higher augmentation index, stiffness index, baseline brachial artery diameter, intima-media thickness, E/E′-ratio, left ventricular (LV) mass/height$^{2.7}$ and relative wall thickness as well as lower flow-mediated dilatation, reactive hyperemia index, and LV ejection fraction compared with individuals not taking VKA.

Accordingly, the concentrations of biomarkers related to cardiac function were higher in anticoagulated compared with nonanticoagulated subjects and there was greater inflammatory activity, as strongly reflected by the elevated concentration of hs-CRP. As proof for the VKA drug effect, activity of vitamin K-dependent coagulation factors was reduced in VKA users and concentrations of hs-D-dimer were ≈50% lower than in VKA-naïve participants (Tables S2 and S3). Concentrations of fibrinogen, however, were increased by 56%.

VKA Intake and Cardiovascular Status in Multivariable Regression Models

In a fully adjusted regression model, controlled for age, sex, and cardiovascular risk factors, the strongest independent associations with VKA use were observed for stiffness index (β=2.54 m/s [0.41; 4.66], *P*=0.019), ankle–brachial index (β=−0.03 [−0.04; −0.01], *P*<0.0001), mean intima-media thickness of the carotid artery (β=0.03 mm [0.01; 0.05], *P*=0.0098), LV ejection fraction of the heart (β=−4.02% [−4.70; −3.33], *P*<0.0001), E/E′ (β=0.04 [0.01; 0.08], *P*=0.014), and LV mass/height$^{2.7}$ (β=5.34 g/m^2 [4.26; 6.44], *P*<0.0001). Vascular function measured by flow-mediated dilatation, reactive hyperemia index, or reflection index was not associated with anticoagulation use (Table 3).

VKA Intake and Humoral Biomarkers in Multivariable Regression Models

A significant positive association with anticoagulation therapy was revealed for midregional pro-adrenomedullin, midregional pro-atrial natriuretic peptide, and N-terminal pro B-type natriuretic peptide as surrogates for the presence of heart failure. hs-CRP and fibrinogen concentrations were positively linked with anticoagulation use (β=0.31 mg/L [0.20; 0.43], *P*<0.0001 and β=143 mg/dL [132; 153], *P*<0.0001, respectively). Again, as proof of the VKA effect, activity levels of FVIII, von Willebrand factor were positively related with VKA use, whereas it was inversely related with FXI activity and hs-D-dimer concentration (Table 4).

Relationship Between Genetic Variants of VKA Metabolism and Surrogate Markers of CVD

Table 5 and Table S4 display the relationship between systematically selected SNPs associated with warfarin

Table 2. Surrogate Parameters of Clinical and Subclinical Cardiovascular Disease

		No Intake of VKA (N=14 564)	Intake of VKA (N=287)
Vasculature	Arterial stiffness		
	Augmentation index, %*	14.43 (3.12/29.03)	16.73 (6.74/31.48)
	Stiffness index, m/s	7.29 (5.78/9.13)	7.72 (6.36/9.26)
	Endothelial function		
	Flow-mediated dilation, %	7.4 (4.6/10.9)	6.0 (3.6/8.4)
	log (reactive hyperemia index)†	0.67 (0.33/0.94)	0.41 (0.13/0.78)
	Reflection index	68 (55/77)	69 (57/78)
	Endothelial structure		
	Baseline BA diameter, mm	4.32 (3.68/4.94)	4.81 (4.19/5.33)
	Intima-media thickness, mm‡	0.63 (0.56/0.73)	0.72 (0.66/0.85)
	Peripheral arterial disease		
	Ankle-brachial index	0.99 (0.93/1.04)	0.97 (0.88/1.06)
Heart	Cardiac function		
	Diastolic function—E/E′ ratio	7.18 (5.90/8.94)	8.33 (6.57/11.31)
	Systolic function—LV ejection fraction, %	63.5 (60.0/67.1)	60.8 (55.0/65.4)
	Cardiac structure		
	LV mass/height$^{2.7}$, g/m$^{2.7}$	36.5 (30.7/43.5)	45.9 (38.6/55.6)
	Relative wall thickness	0.395 (0.345/0.455)	0.424 (0.366/0.490)

For continuous variables, data are expressed as median with 25th/75th percentile. Data were available in >85% of participants, unless otherwise indicated. BA indicates brachial artery; LV, left ventricular; VKA, vitamin K antagonists.
*Measured in a sample of 11 250 participants.
†Measured in a sample of 10 512 participants.
‡Measured in a sample of the first 5000 participants.

maintenance dose and surrogate markers of CVD. *CYP2C9* polymorphisms mainly affected cardiac structure and function among VKA users. Carriers of the minor SNP allele had increased thrombomodulin levels and lower LV mass/height$^{2.7}$ in VKA users, but not in VKA nonusers. Rs2108622 was significantly correlated with an elevated concentration of fibrinogen in VKA users but not in VKA nonusers. The mutant allele of *CYP4F2* rs2108622 was linked to elevated F-XI concentrations and increased LV mass/height,$^{2.7}$ both in VKA users and nonusers, with higher estimates in VKA users.

Subgroup Analysis

In order to evaluate the results in a more homogeneous subgroup, linear regression models controlled for age, sex, and traditional cardiovascular risk factors were performed in individuals with atrial fibrillation and a CHA_2DS_2-VASc score of ≥1 only (see Table S5 for clinical characteristics). The results in this subgroup confirmed the earlier findings (Table S6): VKA therapy was independently related to LV ejection fraction (β=−2.12% [−3.85; −0.38], *P*=0.017), LV mass/height$^{2.7}$ (β=3.61 g/m^2 [0.90; 6.31], *P*=0.0089), midregional pro-atrial natriuretic peptide (β=0.42 pmol/L [0.25; 0.60], *P*<0.0001), N-terminal pro B-type natriuretic peptide (β=1.19 pg/mL [0.73; 1.65], *P*<0.0001), fibrinogen (β=135 mg/dL [112; 157], *P*<0.0001), F-XI (β=−10.8% [−17.5; −4.14], *P*=0.0015), hs-D-dimer (β=−1.07 µg/L [−1.31; −0.84], *P*<0.0001), and hs-CRP (β=0.20 mg/L [0.01; 0.39], *P*=0.035). With regard to arterial stiffness, VKA intake showed a similar effect on stiffness index in this sensitivity analysis as was demonstrated in the unrestricted analysis (β=3.45 m/s [−1.60; 8.50], *P*=0.18). A further propensity score analysis weighted for traditional cardiovascular risk factors and history of cardiovascular diseases in individuals with atrial fibrillation/venous thromboembolism confirmed the robustness of the observations made in the regression analysis (Table S7). To assess possible effects of the duration of VKA treatment on the interrelation between VKA intake and subclinical CVD phenotypes, data were analyzed stratified by the history of drug intake. In brief, hs-CRP concentrations were elevated by 11% when comparing patients with VKA treatment >3 years as opposed to those with shorter treatment. In line with the previous results, arterial stiffness, measured by augmentation index and stiffness index, was higher in individuals with long-term

Table 3. Multivariable Linear Regression Models on the Relationship Between Surrogate Parameters of Clinical and Subclinical Cardiovascular Disease and Therapy With VKA

		β-Estimates for VKA Therapy			
		Adjusted for Age and Sex		Additionally Adjusted for Cardiovascular Risk Factors*	
		β [95% CI]	*P* Value	β [95% CI]	*P* Value
Vasculature	Arterial stiffness				
	Augmentation index, %	−2.12 [−4.61; 0.37]	0.095	−1.23 [−3.66; 1.20]	0.32
	Stiffness index, m/s†	3.39 [1.24; 5.54]	0.0020	2.54 [0.41; 4.66]	0.019
	Endothelial function				
	Flow-mediated dilation, %	−0.11 [−0.75; 0.53]	0.73	0.09 [−0.55; 0.73]	0.79
	log (reactive hyperemia index)	−0.07 [−0.13; −0.01]	0.014	−0.05 [−0.11; 0.01]	0.078
	Reflection index	−0.87 [−2.74; 1.00]	0.36	−0.96 [−2.84; 0.91]	0.31
	Endothelial structure				
	Baseline BA diameter, mm	0.04 [−0.03; 0.11]	0.27	0.005 [−0.07; 0.08]	0.90
	Intima-media thickness, mm	0.03 [0.01; 0.05]	0.0048	0.03 [0.01; 0.05]	0.0098
	Peripheral arterial disease				
	Ankle–brachial index	−0.03 [−0.04; −0.01]	0.00012	−0.03 [−0.04; −0.01]	<0.0001
Heart	Cardiac function				
	Diastolic function—log (E/E′-ratio)	0.06 [0.02; 0.09]	0.0012	0.04 [0.01; 0.08]	0.014
	Systolic function—LV ejection fraction, %	−4.11 [−4.79; −3.43]	<0.0001	−4.02 [−4.70; −3.33]	<0.0001
	Cardiac structure				
	LV mass/height$^{2.7}$, g/m$^{2.7}$	6.27 [5.08; 7.45]	<0.0001	5.34 [4.26; 6.44]	<0.0001
	Relative wall thickness	3.6×10^{-3} [-6.2×10^{-3}; 13.4×10^{-3}]	0.47	-2.7×10^{-3} [-12.3×10^{-3}; 6.9×10^{-3}]	0.58

Effect estimates presented are β-values for VKA use (yes/no) derived from general linear models for each outcome. BA indicates brachial artery; CI, confidence interval; LV, left ventricular; VKA, vitamin K antagonists.
*Cardiovascular risk factors are diabetes mellitus, dyslipidemia, hypertension, obesity, smoking, family history of stroke/myocardial infarction, and estimated glomerular filtration rate.
†Displayed estimates are given for mean age of 55 years; model was additionally adjusted for age×VKA interaction.

exposure to VKA compared with those with short-term exposure, supporting a dose–response relationship (Table 6). For further evaluation of a time-dependent, cumulative effect of VKA intake on subclinical phenotypes of CVD, treatment duration was stratified in <1, 1 to 3, and >3 years as illustrated in Table S8. In brief, the analysis confirmed a dose-dependent interrelation between intake of VKA and specific biomarkers identified in the prior analysis (eg stiffness index, E/E′ ratio, and LV mass).

Discussion

The present study investigated, for the first time, the link between the use of VKA and a comprehensive set of clinical and subclinical measures of CVD in a large population-based sample. The analysis demonstrated a relationship of VKA treatment with increased arterial stiffness, higher LV mass, and decreased cardiac systolic function independent of the clinical profile. Correspondingly, anticoagulation use was also linked with increased concentrations of humoral biomarkers of cardiac function and inflammation. Subgroup analysis confirmed these data: a homogeneous subsample of subjects with atrial fibrillation with indication for oral anticoagulation based on the CHA_2DS_2-VASc score showed consistent results for the comparison of VKA users to anticoagulation-naïve individuals. As an indicator for a dose–response effect, levels of arterial stiffness and hs-CRP were higher in long-term VKA users compared with individuals with shorter intake.

The results from this large population sample are supported by data from the literature: an observational study reported that warfarin administration is associated with a rapid progression of aortic stiffness in patients undergoing hemodialysis.[11] Arterial stiffness is influenced by the calcification of the elastic components of the artery wall, leading to hypertension. In humans, studies of limited sample size have reported an association of VKA treatment with calcification of the coronary arteries.[8,12,13] Also, carotid intima-media

Table 4. Multivariable Linear Regression Models on the Relationship Between Humoral Biomarkers and Therapy With VKA

	β-Estimates for VKA Therapy			
	Adjusted for Age and Sex		Additionally Adjusted for Cardiovascular Risk Factors*	
	β [95% CI]	*P* Value	β [95% CI]	*P* Value
Biomarkers of cardiac function				
log (MR-proANP), pmol/L	0.59 [0.51; 0.67]	<0.0001	0.58 [0.50; 0.65]	<0.0001
log (MR-proADM), nmol/L	0.22 [0.18; 0.27]	<0.0001	0.18 [0.14; 0.22]	<0.0001
log (Nt-proBNP), pg/mL†	1.93 [1.66; 2.19]	<0.0001	1.90 [1.63; 2.17]	<0.0001
Biomarkers of coagulation				
Fibrinogen, mg/dL†	147 [136; 158]	<0.0001	143 [132; 153]	<0.0001
F-VIII, %	15.8 [8.99; 22.7]	<0.0001	13.4 [6.7; 20.2]	<0.0001
F-XI, %	−9.01 [−12.7; −5.30]	<0.0001	−9.63 [−13.31; −5.95]	<0.0001
log (hs-D-dimer), μg/L	−0.89 [−1.02; −0.76]	<0.0001	−0.92 [−1.05; −0.79]	<0.0001
log (thrombomodulin), %	0.04 [−0.04; 0.12]	0.31	0.01 [−0.07; 0.09]	0.76
Tissue factor, %	16.9 [−3.89; 37.7]	0.11	14.7 [−6.0; 35.4]	0.16
vWF, %	13.4 [5.9; 20.9]	0.00047	11.2 [3.8; 18.7]	0.0032
Biomarkers of inflammation				
log (hs-CRP), mg/L	0.42 [0.30; 0.55]	<0.0001	0.31 [0.20; 0.43]	<0.0001
IL-18, pg/mL	23.0 [−0.91; 46.9]	0.059	17.9 [−5.7; 41.5]	0.14
IL-1RA, pg/mL†	36.0 [−10.1; 82.2]	0.13	17.2 [−26.0; 60.3]	0.43
Leukocyte count, /nL	0.03 [−0.001; 0.06]	0.058	0.01 [−0.02; 0.04]	0.39
MPO, pmol/L	33.9 [−1.58; 69.4]	0.061	30.6 [−5.0; 66.2]	0.092

Effect estimates presented are β-values for VKA use (yes/no) derived from general linear models for each outcome. All biomarkers were measured in 5000 participants, except CRP and leukocyte count (available for 15 010 participants). CI indicates confidence interval; hs-CRP, high sensitivity C-reactive protein; MPO, myeloperoxidase; Nt-proBNP, N-terminal pro B-type natriuretic peptide; MR-proADM, midregional pro-adrenomedullin; MR-proANP, midregional pro-atrial natriuretic peptide; VKA, vitamin K antagonists; vWF, von Willebrand factor.
*Cardiovascular risk factors are diabetes mellitus, dyslipidemia, hypertension, obesity, smoking, family history of stroke/myocardial infarction, and estimated glomerular filtration rate.
†Displayed estimates are given for men; model was additionally adjusted for sex (women)×VKA interaction; the estimates for women have to be corrected by adding the following values: Nt-proBNP, −0.95; fibrinogen, +39.0; IL-1RA, +111.

thickness is known to be correlated with atherosclerotic calcification.[14] Interestingly, in the present analysis anticoagulation therapy remained independently related to higher intima-media thickness after adjustment for the clinical profile.

Experimental data indicated that VKA may lead to calcification via inhibition of MGP, a vitamin K-dependent protein produced by vascular smooth muscle cells, which is considered to be a strong inhibitor of vascular calcification.[15] MGP-knockout mice developed soft-tissue calcification resulting in vascular stiffening and died of vascular rupture 8 weeks after birth.[16] Furthermore, both valvular and arterial calcification have been reported in animals on warfarin treatment.[17] By contrast, limited data from experimental animal studies have indicated a potentially beneficial effect of novel, direct-acting anticoagulants on the development and progression of atherosclerosis.[18–20]

Aortic and cardiac valve calcification as well as the abnormal pressure caused by calcification increase cardiac afterload and therefore may promote the development of systolic and diastolic cardiac dysfunction, LV hypertrophy, aortic stenosis, and subsequently congestive heart failure.[21] In the present study, these findings were substantiated by demonstrating an aggravation of cardiac dysfunction in VKA patients compared with the reference group without VKA. Linear regression analyses suggest a link between anticoagulation therapy and an increased LV mass/height$^{2.7}$ ratio, potentially caused by arterial hypertension because of higher stiffness or valve resistance.[22]

The current study demonstrated the presence of elevated concentrations of inflammatory biomarkers (ie hs-CRP, fibrinogen) in individuals on VKA treatment. Previous reports on the inflammation profile of anticoagulated subjects are rare and rather inconsistent. Studies have demonstrated anti-inflammatory effects at low-dose warfarin concentrations in animals[23] and showed little or no effect at the concentration that is used in the clinical setting to reduce hypercoagulability.[24] These studies, however, are prone to

Table 5. SNPs Identified in GWAS Catalogue Known to Influence Warfarin Dose Requirements and Their Relationship to Surrogate Parameters of Atherosclerosis

Selected SNPs From GWAS Catalogue	Chr	Position (Mb)*	Gene	Tag SNP on Affymetrix 6.0 With r^2>0.9	Effect of Minor Allele	Effect Under VKA Use	β Estimate for VKA User†	Effect Under No VKA Use	β Estimate for VKA Nonuser†
rs10509680	10	96734339	*CYP2C9*	rs9332245	Lower	Baseline BA diameter ↑	0.153	Baseline BA diameter ↓	−0.057
					dose	E/E′ ↓	−0.230	E/E′ →	No effect
					requirement				
rs12777823	10	96405502	*CYP2C9*	n.a.	Lower	Fibrinogen ↑	8.7	Fibrinogen ↑	5.6
					dose	Flow-mediated dilation ↓	−0.44	Flow-mediated dilation ↓	−0.46
					requirement	Relative wall thickness ↑	0.05	Relative wall thickness →	No effect
						Ejection fraction ↑	5.54	Ejection fraction →	No effect
						IL-18 ↑	100.8	IL-18 →	No effect
rs4086116	10	96707202	*CYP2C9*	n.a.	Lower	Baseline BA diameter ↓	−0.144	Baseline BA diameter ↓	−0.034
					dose	MR-proADM ↓	−0.057	MR-proADM ↑	0.013
					requirement	IL-18 ↓	−16.6	IL-18 ↑	8.4
						Ejection fraction ↓	−4.27	Ejection fraction →	No effect
						LV mass/height$^{2.7}$ ↑	4.59	LV mass/height$^{2.7}$ →	No effect
rs10871454	16	31048079	*VKORC1*	rs11150604	Lower	Thrombomodulin ↑	0.199	Thrombomodulin ↓	−0.021
					dose	LV mass/height$^{2.7}$ ↓	−2.42	LV mass/height$^{2.7}$ →	No effect
					requirement				
rs2108622	19	15990431	*CYP4F2*	n.a.	Higher	LV mass/height$^{2.7}$ ↑	1.68	LV mass/height$^{2.7}$ ↑	0.48
					dose	F-XI ↑	5.5	F-XI ↑	1.0
					requirement	Fibrinogen ↑	30.47	Fibrinogen →	No effect

BA indicates brachial artery; Chr, chromosome; GWAS, genome-wide association studies; IL-18, interleukin 18; LV, left ventricular; MR-proADM, midregional pro-adrenomedullin; n.a., not available; SNP, single nucleotide polymorphism.
*Based on genome built 105.
†Estimated change per allele.

Table 6. Surrogate Parameters of Clinical and Subclinical Cardiovascular Disease and Humoral Biomarkers According to History of VKA Treatment Length

		3 Y or Less (N=130)	More Than 3 Y (N=130)	Difference
Vascular structure and function	Arterial stiffness			
	Augmentation index, %	14.6 (6.2/29.2)	19.7 (7.6/33.2)	+35%
	Stiffness index, m/s	7.56 (6.12/8.92)	7.89 (6.41/9.58)	+4%
	Endothelial function			
	Flow-mediated dilation, %	6.21 (3.61/8.99)	5.90 (3.63/8.12)	−5%
	Log (reactive hyperemia index)	0.43 (0.10/0.88)	0.34 (0.15/0.74)	−21%
	Reflection-index	66.5 (54.0/77.0)	72.0 (60.3/80.0)	+8%
	Endothelial structure			
	Baseline BA diameter, mm	4.73 (4.08/5.33)	4.95 (4.25/5.33)	+5%
	Intima-media thickness, mm	0.72 (0.63/0.84)	0.73 (0.68/0.85)	+2%
	Peripheral arterial disease			
	Ankle–brachial index	0.97 (0.89/1.04)	0.97 (0.88/1.07)	0%
Cardiac structure and function	Cardiac function			
	E/E′-ratio	8.02 (6.32/10.03)	8.73 (6.80/12.38)	+9%
	Ejection fraction, %	61.1 (55.4/66.4)	60.0 (53.7/65.1)	−2%
	Cardiac structure			
	LV mass/height$^{2.7}$, g/m$^{2.7}$	45.6 (37.2/54.5)	47.6 (38.9/56.9)	+4%
	Relative wall thickness	0.429 (0.371/0.489)	0.417 (0.365/0.507)	−3%
Humoral biomarker	Biomarker of coagulation			
	Fibrinogen, mg/dL	506 (438/584)	500 (428/588)	−1%
	Biomarker of inflammation			
	hs-CRP, mg/L	2.65 (1.20/5.50)	2.95 (1.30/5.42)	+11%
	Leukocytes, /nL	7.08 (5.93/8.20)	7.30 (6.19/8.50)	+3%

For continuous variables, data are expressed as median with 25th/75th percentile. The percentage differences represent an increase or decrease going from "VKA use of 3 y or less" to "VKA use of more than 3 y." BA indicates brachial artery; hsCRP, high-sensitivity C-reactive protein; LV, left ventricular; VKA, vitamin K antagonists.

methodological limitations including small sample sizes. Importantly, it is well recognized that coagulation factors play a significant role in the process of inflammation and atherosclerosis.[25] The attenuation of protein C has been reported to reduce anti-apoptotic activity of the endothelial barrier and to promote local inflammation within the arterial wall,[25] which is accompanied, at least to a certain degree, by calcification.[26] In addition, infiltration of vascular tissue is characterized by increased oxidative stress and subsequently by endothelial dysfunction leading to increased vascular stiffness.[27] Coumarin derivatives including phenprocoumon have been shown to act as sepiapterin reductase inhibitors leading to intracellular tetrahydrobiopterin (BH_4) depletion.[28] Endothelial BH_4 depletion in turn may reduce vascular nitric oxide production or even cause endothelial nitric oxide synthase uncoupling associated with endothelial dysfunction and therefore higher vascular production of reactive oxygen species within the vascular wall.[29] Thus, the resulting reduction in vascular nitric oxide bioavailability may also contribute to increased vascular stiffness. VKA also inhibit the carboxylation of Gas-6, which protects vascular smooth muscle cells from calcification by inhibiting apoptosis.[30] This may have contributed to the enhanced inflammation observed in the present study. Therefore, one might speculate that VKA cause inflammation and apoptosis of vascular smooth muscle cells while simultaneously reducing endothelial nitric oxide production, which could potentially accelerate the process of vascular and cardiac damage. It merits consideration that the influence of VKA treatment may affect specific vascular beds differently (eg according to the content of VKA-dependent extracellular matrix protein Gla), which may also impact on the subsequent clinical outcome.[31] As an interconnecting link, the increased level of systemic inflammation upon VKA intake may serve as a potential explanation for VKA-induced propagation of (subclinical) atherosclerosis and cardiovascular disease.

Finally, the effect of genetic polymorphisms associated with VKA dosing surrogate markers for prevalent CVD was investigated. Genome-wide association studies have identified the association of CYP2C9, VKORC1, and CYP4F2 SNPs with stable VKA dosing.[32] Interestingly, comparable effects of gene variants on enzyme activity did not always match with homogeneous effects on cardiac structure and function, and inflammation. Among VKA users and VKA-naïve subjects, SNPs affecting the VKA dosing translated into different effects on subclinical and humoral markers of CVD. The influence of VKA metabolism indicates that VKA therapy has a link to CVD progression, rather than an underlying CVD. Although these analyses do not provide sufficient evidence to avoid the use of VKA in patients susceptible to deterioration of cardiac and vascular function, the potential implication for individualized antithrombotic therapy merits further investigation, especially in comparison to direct inhibition of FIIa and FXa, respectively.

Limitations

There are several limitations that need to be considered when interpreting the data of the present study. First, the cross-sectional design does not allow for making any inferences about cause and effect. Prospective data covering an adequate period of exposure to VKA is necessary to analyze the effects of VKA on atherosclerosis over time. Second, although a large panel of potential confounders was adjusted for in regression analysis, the possibility that unmeasured confounders might have contributed to the observed findings cannot be excluded. Third, information on serum concentrations of MGP and Gas-6 were not available for the present study, but rather likely biological sequelae were investigated. Fourth, individuals receiving novel, direct-acting anticoagulants for oral anticoagulation therapy were not available for comparison at a statistically adequate sample size in the study sample. Fifth, the limited sample size did not allow providing specific subgroup analysis for potentially vulnerable patient populations (eg patients with type 2 diabetes mellitus). Sixth, parts of the findings of the present study confirm prior investigations on the associations of VKA and subclinical markers of CVD. Finally, the results may not be extrapolated to populations of other ethnic backgrounds as allele frequencies of CYP2C9 and VKORC1 vary among ethnic groups.

Conclusions

In summary, the present investigation indicates an independent association between the use of VKA and surrogate parameters of arterial stiffness, vascular morphology, cardiac structure and function, and inflammation in the population. Given the high coprevalence of oral anticoagulation therapy with (sub)clinical atherosclerosis and the increasing need for antithrombotic agents in the future, these findings may have implications for individually tailored approaches for antithrombotic therapy.

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SUPPLEMENTAL MATERIAL

DATA S1.

SUPPLEMENTAL METHODS

Cardiovascular phenotyping

All study-related actions including medical and technical measurements were performed according to standard operating procedures (SOP) by specifically trained and certified medical technical assistants. Digital Imaging data were recorded on a server with an integrated multi-modality image management system (Xcelera, Royal Philips Electronics, Amsterdam, The Netherlands).

Intima media thickness (IMT) was assessed with an iE33 ultrasound system (Philips Medical Systems, Best, The Netherlands) using a computerized edge detection system (Qlab software, Royal Philips, The Netherlands) with triggering according to the Q wave in electrocardiography. IMT was measured at both common carotid arteries (CCAs). Mean IMT was recorded 1 cm proximal to the carotid bulb over a length of 1 cm at the far wall and only in vessel segments without plaques.

Vascular function by ultrasound (flow-mediated dilation; FMD) was measured according to a standard protocol: after a 5-minute supra-systolic upper arm occlusion, diameter measurements of the brachial artery were performed on two-dimensional high-resolution ultrasound images recorded on a Philips HD11XE CV ultrasound machine (Philips, Best, Netherlands) using a linear array broadband probe, L12–5 (38 mm). Participants were in resting conditions of at least 5 minutes before the measurements. Diameters were measured offline using the commercially available Brachial Analyzer software package, version 5.0 (Medical Imaging Applications LLC, Iowa City, US). The means of three measurements at baseline and at 60 seconds after cuff release were taken for analysis.

Reflection index reflecting vascular tone of arteries and stiffness index reflecting artery stiffness were measured by PulseTrace 2000 device (Cardinal Health/Micro Medical Limited, Rochester, United Kingdom). The digital volume pulse was obtained by averaging the transmission of infrared light of ten pulse waves through the pulp of the right ring finger.

Peripheral Arterial Tonometry (PAT) was recorded by the Endo-PAT2000 fingertip device (Itamar Medical, Caesarea, Israel). Baseline pulse amplitude was measured electronically in both index fingers, with the left index finger serving as a control. The PAT-ratio was automatically calculated using a computerized algorithm.

All subjects underwent multimodal echocardiography with an iE33 echocardiography system with an S5–1 sector array transducer (Royal Philips Electronics, Amsterdam, The Netherlands). Cardiac structure was assessed by two-dimensional guided M-mode measurements of the parasternal long axis view of the left ventricle (LV). Left ventricular

mass and relative wall thickness (RWT) were calculated from LV diastolic internal dimension (LVDD), intraventricular septum diameter (IVSD) and LV posterior wall thickness (LVPWD). Cardiac function was assessed by biplane LV ejection fraction (LVEF in %) according to the modified Simpson method in 4- and 2-chamber views. The E/E' ratio as surrogate for diastolic function was calculated by dividing the early filling velocity of transmitral Doppler (E) by the early relaxation velocity on tissue Doppler (E').

Definitions of Cardiovascular Risk Factors and Comorbidities

Arterial hypertension was stated for participants, who at least hold one of the following conditions: a) Intake of hypertensive drugs b) mean systolic blood pressure ≥ 140 mm Hg c) mean diastolic blood pressure ≥ 90 mm Hg or d) definite diagnosis of hypertension by physician. Antidiabetic drug treatment, a fasting blood glucose level ≥ 126 mg/dl after overnight fasting of at least 8 hours, a blood glucose level of ≥ 200 mg/dl after a fasting period of at least 8 hours at the baseline examination or a physician diagnosis of diabetes lead to the diagnosis of diabetes. Dyslipidemia was defined on intake of lipid lowering drugs, a LDL / HDL-ratio of ≥ 3.5 or a definite diagnosis of dyslipidemia by a physician. Smoking was dichotomized into smokers (occasional smokers and smokers) and non-smokers (never smokers and ex-smokers). Anthropometric measurements were taken with calibrated digital scales (Seca 862, Seca, Hamburg, Germany), a measuring stick (Seca 220, Seca, Hamburg, Germany) and a non-stretching waist measuring tape. Waist circumference was measured midway between the lower rib margin and the superior anterior iliac spine. Body height and weight were measured without shoes in underwear and the body mass index (BMI) was calculated as weight in kilograms divided by the scare of height in meters. Obesity was determined as BMI ≥ 30 kg/ m² according to WHO criteria. A positive family history of myocardial infarction or stroke was defined as at least one myocardial infarction or stroke in a female first-degree relative before 65 years of age and in a male first-degree relative before 60 years of age.

The diagnosis of Atrial Fibrillation (AF) was based on the history of AF reported by the participant during the computer assisted interview and/or the evidence of AF on the resting electrocardiogram (ECG) and/or the documentation of AF on the echocardiogram performed during the study. At least two physicians with training and experience in ECG reading had to confirm the diagnosis. Cancer, chronic obstructive pulmonary disease, congestive heart failure, coronary artery disease, deep vein thrombosis, liver disease, myocardial infarction, peripheral arterial disease, pulmonary embolism, and stroke were assessed by self-report of the participants and were collected by computer-assisted personal interviews. Chronic kidney

disease was defined as an estimated glomerular filtration rate of less than 60 ml/min/1.73m² assess by a urine sample taken at the study center.

Genotyping and imputation of single nucleotide polymorphism

The search in the GWAS catalogue, accessed on 25th July 2015, resulted in four studies with 11 warfarin metabolism related SNPs. The genetic variants have been investigated in detail; inconsistent results were identified and not considered for further analysis. Two SNPs were present on the Affymetrix array used in this study. The other eight SNPs were tested with SNP Annotation and Proxy Search (http://www.broadinstitute.org/mpg/snap/ldsearch.php) for one or several proxies in linkage disequilibrium (LD) on the array. The following search options were used: r2 threshold = 0.9, distance limit = 500, population panel = CEU, SNP data set = 1000 Genomes Pilot 1. Overlapping SNPs were excluded from the analysis. For two GWAS SNPs no matching proxy could be found on the Affymetrix 6.0 Array, resulting in five warfarin maintenance dose related SNPs (**Table 7**).

Table S1. Use of medication according to VKA intake

	No VKA intake (N= 14,564)	Intake of VKA (N=287)	Prevalence ratio
Antidiabetics	6.0 (879)	15.3 (44)	2.6
Antiplatelet agents	10.3 (1499)	9.1 (26)	0.9
Beta-blockers	16.2 (2357)	61.7 (177)	3.8
Calcium channel blockers	7.0 (1024)	22.6 (65)	3.2
Diuretics	4.8 (705)	29.3 (84)	6.1
Lipid modifying drugs	12.8 (1862)	41.5 (119)	3.2
Statins	11.2 (1628)	39.7 (114)	3.3
Fibrates	0.7 (100)	2.1 (6)	3.0
Other lipid modifying agents	1.2 (168)	5.9 (17)	3.2
Low-molecular-weight heparins	0.1 (18)	1.7 (5)	17.0
Renin angiotensin aldosterone system inhibitors	23.1 (3358)	64.1 (184)	2.8

Data are expressed as median with 25th/75th percentile. The prevalence ratio was calculated as the ratio of the frequency for “Intake of VKA” to the one for “No VKA intake”.

Table S2. Vitamin K dependent proteins and laboratory tests according to VKA intake

	No VKA intake (N= 14,564)	Intake of VKA (N=287)	Difference
FII [%]	117.5 (105.5/130.1)	33.0 (27.9/39.9)	-72%
FVII [%]	111.8 (99.7/129.3)	33.9 (29.7/43.8)	-70%
FIX [%]	111.8 (101.5/122.4)	58.7 (49.8/70.6)	-47%
FX [%]	115.9 (103.6/130.1)	18.0 (13.6/22.8)	-84%
Protein C [%]	117.5 (105.0/131.0)	52.6 (47.2/61.5)	-55%
Protein S [%]	101.8 (90.2/114.2)	49.8 (42.2/56.4)	-51%
aPTT [s]	30.2 (28.4/32.3)	46.2 (40.6/50.5)	+53%
INR	1.00 (1.00/1.00)	2.50 (2.10/2.90)	+150%

Data are expressed as median with 25^{th}/75^{th} percentile. Significant difference between the groups (P <0.0001) was detected for all outcomes. The percentage differences represent the change between “Intake of VKA” compared to “No VKA intake”.

Table S3. Profile of humoral biomarkers by VKA use

	No VKA intake (N= 14,564)	Intake of VKA (N=287)	Difference
Biomarkers of cardiac function			
MR-proANP [pmol/L]	65.3 (48.7/88.8)	145.6 (98.9/229.7)	+123%
MR-proADM [nmol/L]	0.46 (0.39/0.54)	0.64 (0.55/0.78)	+39%
Nt-proBNP [pg/mL]	60.4 (27.8/119.6)	514.4 (141.9/1256.2)	+752%
Biomarkers of coagulation			
Fibrinogen [mg/dl] ‡	320 (277/372)	500 (428/586)	+56%
F-VIII [%]	120.60 (100.30/141.28)	139.25 (120.84/161.06)	+15%
F-XI [%]	109.0 (97.5/122.5)	101.5 (89.2/112.6)	-7%
hs-D-dimer [µg/L]	229 (149/352)	122 (66/210)	-47%
Thrombomodulin [%]	1.99 (1.62/2.45)	2.03 (1.73/2.65)	+2%
Tissue factor [%]	200 (160 /250)	237 (192/280)	+18%
vWF [%]	106.8 (81.5/137.2)	138.6 (106.1/159.0)	+30%
Biomarkers of inflammation			
hs-CRP [mg/l] ‡	1.50 (0.54/3.20)	2.70 (1.30/5.40)	+80%
IL-18 [pg/ml]	217 (168/283)	243 (193 /337)	+12%
IL-1RA [pg/ml]	319 (239/425)	367 (285/487)	+15%
Leukocyte count [10^9/L] *	6.90 (5.82/8.26)	7.20 (6.07/8.33)	+4%
MPO [pmol/L]	296 (234/371)	345 (265/428)	+17%

MR-proANP, Mid-regional Pro-Atrial Natriuretic Peptide; MR-proADM, Midregional Pro-Adrenomedullin; Nt-proBNP, N-terminal pro-brain natriuretic peptide; vWF, von Willebrand factor; hs-CRP, high sensitivity C-reactive protein; IL-18, interleukin-18; IL-1RA, interleukin-1 receptor antagonist; MPO, myeloperoxidase;

Data are expressed as median with $25^{th}/75^{th}$ percentile. The percentage differences represent the change between "Intake of VKA" compared to "No VKA intake".

All biomarkers were measured in a sample set of the first 5,000 participants, unless otherwise indicated. * measured in a sample set of 15,010 participants

Table S4. SNPs identified in GWAS catalogue known to influence warfarin dose requirements

Selected SNPs form GWAS catalogue	Chr	Position (Mb) ‡	Gene	Tag SNP on Affymetrix 6.0 with $r^2 > 0.9$	r^2 between lead SNP and tag SNP	Distance between lead SNP and tag SNP (KB)	Minor allele	MAF †	Effect of minor allele
rs10509680	10	96734339	*CYP2C9*	rs9332245	1.00	14842	A	0.058	Lower dose requirement
rs12777823	10	96405502	*CYP2C9*	n.a	n.a	n.a	A	0.169	Lower dose requirement
rs4086116	10	96707202	*CYP2C9*	n.a	n.a	n.a	T	0.205	Lower dose requirement
rs10871454	16	31048079	*VKORC1*	rs11150604	1,00	11059	T	0.398	Lower dose requirement
rs2108622	19	15990431	*CYP4F2*	n.a	n.a	n.a	T	0.232	Higher dose requirement

SNP, single nucleotide polymorphism; GWAS, genome-wide association studies; MAF, Minor allele frequency

‡ based on genome built 105

† based on HapMapCEU data (http://www.ncbi.nlm.nih.gov.snp)

Table S5. Baseline characteristic in the subgroup of participants with atrial fibrillation and indication for oral anticoagulation stratified for VKA use (diagnosis of atrial fibrillation and CHA2DS2-VASc Score of ≥ 1)

	No VKA intake (N= 263)	Intake of VKA (N=158)
Age [years]	68.0 (63.0/71.0)	68.0 (64.0/72.0)
Sex (Female)	33.8 (89)	28.5 (45)
Traditional cardiovascular risk factors		
Diabetes mellitus	18.6 (49)	19.0 (30)
Dyslipidemia	43.7 (114)	44.9 (71)
Family history of myocardial infarction /stroke	27.8 (73)	22.2 (35)
Hypertension	81.4 (214)	80.4 (127)
Obesity	37.6 (99)	39.9 (63)
Smoking	12.2 (32)	12.8 (20)
Comorbidities		
Cancer	16.8 (44)	17.7 (28)
Chronic kidney disease	9.9 (26)	17.7 (28)
Chronic obstructive pulmonary disease	11.4 (30)	11.4 (18)
Congestive heart failure	9.9 (26)	20.3 (32)
Coronary artery disease	23.3 (58)	27.3 (41)
Deep vein thrombosis	8.1 (21)	12.8 (20)
Liver disease	1.1 (3)	1.3 (2)
Myocardial infarction	15.7 (41)	19.0 (29)
Peripheral artery disease	8.6 (22)	10.8 (17)
Pulmonary embolism	0 (0)	0.6 (1)
Stroke	5.7 (15)	16.3 (25)

Data are expressed as the relative and absolute frequencies for binary variables, for continuous variables as median with $25^{th}/75^{th}$ percentiles. The prevalence ratio was calculated as the ratio of the frequency for “Intake of VKA” to the one for “No VKA intake”.

Table S6. Multivariable linear regression models on the relationship between surrogate parameters of subclinical cardiovascular disease and humoral biomarkers in the subgroup of participants with atrial fibrillation and a CHA_2DS_2-VASc Score of ≥ 1

		β - estimates with corresponding 95% CI for VKA use		
		Adjusted for age, sex and cardiovascular risk factors *		
		β	95% CI	*P*-Value
Vascular structure and function	*Arterial stiffness*			
	Augmentation index [%]	-0.81	-4.93; 3.32	0.70
	Stiffness index [m/s] †	3.45	-1.61; 8.51	0.18
	Endothelial function			
	Flow- mediated dilation [%]	-0.76	-1.73; 0.21	0.12
	log (Reactive hyperemia index)	**-0.11**	**-0.21**; **-0.01**	**0.025**
	Reflection-Index	-0.03	-3.77; 3.71	0.99
	Endothelial structure			
	Baseline brachial artery diameter [mm]	-0.02	-0.15; 0.12	0.80
	Intima-media thickness [mm]	0.01	-0.03; 0.05	0.65
	Peripheral arterial disease			
	Ankle brachial-index	-0.01	-0.04; 0.02	0.58
Cardiac structure and function	*Cardiac function*			
	log (E/E´-ratio)	0.03	-0.04; 0.11	0.39
	LV ejection fraction [%]	**-2.12**	**-3.85**; **-0.38**	**0.017**
	Cardiac structure			
	LV mass/ height$^{2.7}$ [g/m$^{2.7}$]	**3.61**	**0.90**; **6.31**	**0.0089**
	Relative wall thickness	0.01	-0.01; 0.03	0.45
Humoral biomarkers	*Biomarkers of cardiac function*			
	log (MR-proANP) [pmol/L]	**0.42**	**0.25**; **0.60**	**< 0.0001**
	log (MR-proADM) [nmol/L]	0.06	-0.01; 0.14	0.085
	log (Nt-proBNP) [pg/mL] ‡	**1.19**	**0.73**; **1.65**	**< 0.0001**
	Biomarkers of coagulation			
	Fibrinogen [mg/dl] ‡	**135**	**112**; **157**	**< 0.0001**
	FVIII [%]	3.18	-9.75; 16.1	0.63
	FXI [%]	**-10.8**	**-17.5**; **-4.14**	**0.0015**
	log (hs-d-Dimer) [µg/L]	**-1.07**	**-1.31**; **-0.84**	**< 0.0001**
	log (Thrombomodulin) [%]	0.10	-0.06; 0.26	0.22
	Tissue factor [%]	2.4	-32.1; 36.9	0.89
	vWF [%]	5.3	-9.1; 19.8	0.47

Table S6. (continued)

	β - estimates with corresponding 95% CI for VKA use		
	Adjusted for age, sex and cardiovascular risk factors *		
	β	95% CI	*P*-Value
Biomarkers of inflammation			
log (hs-CRP) [mg/l]	**0.20**	**0.01**; **0.39**	**0.035**
IL-18 [pg/ml]	29.6	-24.2; 83.3	0.28
IL-1RA [pg/ml] ‡	26.9	-77.1; 131	0.61
log (Leukocyte count) [10^9/L]	0.0008	-0.05; 0.05	0.97
MPO [pmol/L]	43.8	-27.0; 115	0.23

* Cardiovascular risk factors include diabetes mellitus, dyslipidemia, hypertension, obesity, smoking, family history of stroke/myocardial infarction, eGFR

† displayed estimates are given for mean age of 64.5 years; model was additionally adjusted for age*VKA interaction

‡ displayed estimates are given for men; model was additionally adjusted for sex(women)*VKA interaction; consequently the estimates for women have to be corrected by adding the following values: Nt-proBNP, +0.42; fibrinogen, +28.2; IL-1RA, +99.9. LV, left ventricular.

Table S7. Parameters of cardiovascular function and structure by VKA intake in propensity score weighted sample of individuals with atrial fibrillation or venous thrombosis

		No intake of VKA (N= 226)	Intake of VKA (N=224)
Vasculature	*Arterial stiffness*		
	Augmentation index [%]	18.91 (8.49/31.75)	14.73 (6.46/26.61)
	Stiffness index [m/s]	8.25 (6.55/9.96)	7.91 (6.50/9.40)
	Endothelial function		
	Flow- mediated dilation [%]	6.69 (4.10/8.97)	6.16 (3.90/8.59)
	log (Reactive hyperemia index)	0.47 (0.23/0.82)	0.41 (0.12/0.77)
	Reflection-Index	72.00 (57.54/79.00)	67.00 (55.92/78.00)
	Endothelial structure		
	Baseline brachial artery diameter [mm]	4.83 (4.30/5.32)	4.80 (4.16/5.33)
	Intima-media thickness [mm]	0.72 (0.65/0.83)	0.73 (0.66/0.85)
	Peripheral arterial disease		
	Ankle brachial-index	0.99 (0.91/1.05)	0.98 (0.89/1.06)
Heart	*Cardiac function*		
	log (E/E´-ratio)	8.37 (6.65/10.29)	8.26 (6.50/10.79)
	LV ejection fraction [%]	62.5 (58.7/66.7)	60.9 (55.2/65.4)
	Cardiac structure		
	LV mass/ height$^{2.7}$ [g/m$^{2.7}$]	43.0 (35.8/51.2)	45.7 (38.4/55.4)
	Relative wall thickness	0.42 (0.37/0.49)	0.43 (0.37/0.50)
Humoral biomarkers	*Biomarkers of cardiac function*		
	log (MR-proANP) [pmol/L]	95.7 (65.9/141.0)	151.0 (106.6/240.4)
	log (MR-proADM) [nmol/L]	0.61 (0.50/0.72)	0.63 (0.55/0.75)
	log (Nt-proBNP) [pg/mL]	132 (58/292)	554 (208/1270)
	Biomarkers of coagulation		
	Fibrinogen [mg/dl]	349 (295/411)	498 (431/591)
	FVIII [%]	133.5 (112.1/154.1)	138.4 (120.1/152.7)
	FXI [%]	108.5 (96.9/120.4)	101.0 (87.4/112.6)
	log (hs-d-Dimer) [µg/L]	374.8 (230.9/624.3)	120.0 (62.5/213.7)
	log (Thrombomodulin) [%]	2.09 (1.83/2.64)	2.04 (1.72/2.64)
	Tissue factor [%]	206.9 (167.5/259.1)	230.8 (195.5/276.2)
	vWF [%]	125.0 (95.1/153.4)	139.4 (106.1/159.9)
	Biomarker of inflammation		
	Hs-CRP [mg/l]	2.30 (1.20/4.30)	2.60 (1.24/5.50)
	IL-18 [pg/ml]	246.1 (185.3/311.8)	248.7 (199.5/338.6)
	IL-1RA [pg/ml]	350.0 (260.8/458.1)	366.2 (279.7/489.8)
	Leukocytes [/nl]	7.10 (6.13/8.47)	7.16 (6.08/8.32)
	MPO [pmol/L]	320.8 (244.8 /380.9)	333.7 (249.9/412.7)

Inverse probability of treatment weighting using the propensity score was applied. The underlying propensity model included age, sex, diabetes mellitus, obesity, smoking, arterial hypertension, dyslipidemia, family history of stroke or myocardial infarction and history of cardiovascular diseases. All standardized differences for those variables between treatment groups after weighting were <0.1.

Table S8. Parameters of cardiovascular function and structure by VKA exposure time

		< 1 year (N=64)	1-3 years (N=66)	> 3 years (N=130)
Vasculature	*Arterial stiffness*			
	Augmentation index [%]	14.5 (6.3 /26.6)	16.7 (5.7 /31.1)	19.7 (7.6/33.2)
	Stiffness index [m/s]	7.47 (6.25/8.82)	7.65 (6.06/9.20)	7.89 (6.41/9.58)
	Endothelial function			
	Flow- mediated dilation [%]	5.54 (3.65/9.06)	7.04 (3.56/8.96)	5.90 (3.63/8.12)
	Log (Reactive hyperemia index)	0.63 (0.29/0.92)	0.26 (0.06/0.72)	0.34 (0.15/0.74)
	Reflection-Index	65.0 (54.0/75.0)	67.0 (55.2/77.0)	72.0 (60.3/80.0)
	Endothelial structure			
	Baseline BA diameter [mm]	4.68 (4.02/5.32)	4.75 (4.20/5.33)	4.95 (4.25/5.33)
	Intima-media thickness [mm]	0.78 (0.56/0.94)	0.71 (0.66/0.77)	0.73 (0.68/0.85)
	Peripheral arterial disease			
	Ankle brachial- index	0.98 (0.88/1.05)	0.97 (0.90/1.04)	0.97 (0.88/1.07)
Heart	*Cardiac function*			
	E/E´-ratio	7.90 (6.22/9.96)	8.25 (6.37/10.51)	8.73 (6.80/12.38)
	Ejection fraction [%]	59.2 (53.7/64.5)	62.3 (57.0/66.7)	60.0 (53.7/65.1)
	Cardiac structure			
	LV mass/ height$^{2.7}$ [g/m$^{2.7}$]	41.9 (36.2/52.2)	48.7 (42.5/59.2)	47.6 (38.9/56.9)
	Relative wall thickness	0.43 (0.35/0.50)	0.43 (0.38/0.48)	0.42 (0.37/0.51)
Humoral Biomarker	*Biomarker of coagulation*			
	Fibrinogen [mg/dl]	484 (429/570)	518 (456/593)	500 (428/588)
	Biomarker of inflammation			
	Hs-CRP [mg/l]	2.55 (1.14/4.80)	2.70 (1.59/6.43)	2.95 (1.30/5.42)
	Leukocytes [/nl]	7.28 (6.00/8.90)	6.78 (5.86/7.80)	7.30 (6.19/8.50)

Direct oral anticoagulants and vitamin K antagonists are linked to differential profiles of cardiac function and lipid metabolism

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ORIGINAL PAPER

Direct oral anticoagulants and vitamin K antagonists are linked to differential profiles of cardiac function and lipid metabolism

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Abstract

Background Experimental data indicate that direct acting oral anticoagulants (DOAC) and vitamin K antagonists (VKA) may exert differential effects on cardiovascular disease.

Methods Data from the prospective, observational, single-center MyoVasc Study were used to examine associations of DOAC as compared to VKA with subclinical markers of cardiovascular disease, cardiac function, and humoral biomarkers in heart failure (HF).

Results Multivariable analysis adjusted for age, sex, traditional cardiovascular risk factors, comorbidities, and medications with correction for multiple testing demonstrated that DOAC therapy was among all investigated parameters an independent significant predictor of better diastolic function (E/E': $\beta -0.24$ [−0.36/−0.12]; $P<0.0001$) and higher levels of ApoA1 ($\beta+0.11$ g/L [0.036/0.18]; $P=0.0038$) compared to VKA therapy. In propensity score-weighted analyses, the most pronounced differences between DOAC and VKA-based therapy were also observed for E/E' ($\Delta -2.36$) and ApoA1 ($\Delta +0.06$ g/L). Sensitivity analyses in more homogeneous subsamples of (i) individuals with AF and (ii) individuals with asymptomatic HF confirmed the consistency and robustness of these findings. In the comparison of factor IIa and Xa-directed oral anticoagulation, no differences were observed regarding cardiac function (E/E' ratio: $\beta_{\text{IIa inhibitor}}$ −0.22 [−0.36/−0.08] vs. $\beta_{\text{Xa inhibitor}}$ −0.24 [−0.37/−0.11]) and lipid metabolism (ApoA1: $\beta_{\text{IIa inhibitor}}$ 0.10 [0.01/0.18] vs. $\beta_{\text{Xa inhibitor}}$ 0.12 [0.04/0.20]) compared to VKA therapy.

Conclusion This study provides the first evidence for differential, non-conventional associations of oral anticoagulants on cardiac function and lipid metabolism in humans. The potentially beneficial effect of DOACs in the highly vulnerable population of HF individuals needs to be further elucidated and may have implications for individually tailored anticoagulation therapy.

Keywords Anticoagulation · Direct oral anticoagulants · Vitamin K antagonist · Cardiac function · Lipids and lipid protein metabolism

Introduction

Anticoagulation therapy with vitamin K antagonist (VKA) has represented one of the cornerstones of antithrombotic therapy for decades [1]. The introduction of direct acting oral anticoagulants (DOAC) has considerably changed the landscape and broadened the options for oral anticoagulant therapy in daily clinical routine [2, 3]. Since a wide therapeutic arsenal to interfere with clot formation is now available, individualized antithrombotic therapy requires integrating information on both patient characteristics and knowledge on the specific effects of anticoagulant agents.

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The activity of thrombin (factor IIa), an enzyme responsible for converting prothrombin to thrombin, or factor Xa can be directly inhibited by DOAC (e.g., dabigatran, rivaroxaban, apixaban, and edoxaban). Alternatively, VKA exert their anticoagulant effect by inhibiting vitamin K epoxide reductase, thereby limiting the cofactor effect of vitamin K on the γ-carboxylation of the vitamin K-dependent coagulation factors II, VII, IX, and X. In addition to the hemostatic effects of oral anticoagulants in the prevention and treatment of thrombosis, the previous studies have indicated the potential for differential non-canonical effects of anticoagulants through cellular protease-activated receptors (PARs) in various cell types (e.g., vascular smooth muscle cell, platelets, fibroblasts, and endothelial cells) [4]. Pre-clinical and clinical studies investigating non-coagulant effects of DOACs have indicated potential effects of these drugs beyond their primary antithrombotic action including an inhibitory effect on the development of atherosclerosis and the onset of atrial fibrillation [4, 5]. In the COMPASS trial, the application of low-dose factor Xa inhibitor rivaroxaban on top of aspirin to patients with stable cardiovascular disease reduced the incidence of major adverse cardiovascular and limb events, indicating a beneficial effect on the course of atherosclerotic cardiovascular disease [6]. In pre-clinical studies, it has been demonstrated that the direct inhibition of factor Xa or thrombin may contribute to anti-inflammatory actions and an attenuation of atherosclerosis [7–14]. Experimental studies have reported that direct thrombin inhibition reduces the formation and lesion size of atherosclerotic plaques and improves endothelial function in apolipoprotein E-deficient mice [9–11, 15]. Direct thrombin inhibition has also been shown to interfere with lipid metabolism by reducing levels of apolipoprotein B (ApoB) [16] and to potentially affect cardiac function and cardiac remodeling [13, 17–20]. In contrast to direct inhibitors of factor Xa and thrombin, VKAs are known to not only affect the carboxylation of vitamin K-dependent coagulation factors, but also the action of matrix Gla protein, resulting in calcification of heart valves and vessels leading to arterial stiffness [21, 22].

Given this body of evidence, which is mostly derived from experimental studies, we hypothesized that DOAC- and VKA-based antithrombotic regimes exert differential effects on cardiovascular structure and function in humans via different mechanistic pathways [23]. Evidence is limited with regard to pleiotropic effects of DOACs and VKA in humans, especially for individuals with heart failure who may be particularly susceptible to these effects due to the contributory effect of underlying diseases. The aim of the current study was to compare the effects of DOAC- and VKA-based anticoagulation therapy on intermediate phenotypes of cardiovascular disease in individuals with heart failure.

Methods

Study design

The MyoVasc Study is an investigator-initiated, prospective, single-center cohort study, which is conducted at the University Medical Center of the Johannes Gutenberg-University Mainz, Germany. The study is led by an academic steering committee and was designed according to the tenets of the revised Helsinki protocol. Approval of the local ethics committee (medical association Rhine-Hesse, Germany) and of the local data safety commissioner was obtained before study initiation. All study participants provided written informed consent before study enrolment. Study participants were recruited from a mid-western population of predominant white European ancestry.

From January 2013 to January 2016, 2000 individuals with stable heart failure were recruited to the MyoVasc study fulfilling the following inclusion criteria: (i) 35–84 years of age; (ii) asymptomatic or symptomatic cardiac dysfunction; and (iii) absence of acute cardiac disease (i.e., endocarditis, myocarditis, pericarditis, acute cardiac decompensation, and acute myocardial infarction) and of acute infections. For the present analysis, study participants with an intake of oral anticoagulants (assessed according to ATC coding at the initial visit in the study center) were selected.

Data assessment

At the baseline visit in the study center, study participants underwent a physical examination by a qualified physician, highly standardized deep clinical phenotyping comprising a 5-h clinical investigation (e.g., ECG, 2D-, and 3D-cardiac echocardiography, sonography of the carotid artery, and assessment of vascular function) and comprehensive blood withdrawal for biobanking. For the present analysis, distinct non-invasively measured intermediate phenotypes of cardiovascular structure and function were analyzed comprising stiffness index (measured by Pulse Trace 2000, Micro Medical Ltd., Rochester, United Kingdom), left ventricular ejection fraction, E/E' ratio, left ventricular mass, and relative wall thickness (measured during echocardiography) [24, 25]. Left ventricular dimensions and wall thickness were determined in parasternal long axis. Left ventricular mass was calculated from the linear dimensions in the parasternal long axis view or M-mode. Left ventricular ejection fraction was calculated using the Simpson's method in apical four-chamber view. During Doppler recording of the mitral inflow, measurement of peak velocity of early diastolic filling (E) was performed,

whereas peak longitudinal early diastolic velocity (E') was measured in pulsed wave tissue Doppler imaging recordings at the lateral mitral annulus. All echocardiographic parameters were assessed by a Philips iE33 ultrasound system using an S5-1 sector array transducer (Philips Medical Systems, The Netherlands) and were performed according to current guideline recommendations [25]. During a computer-assisted personal interview, information on cardiovascular risk factors, comorbidities, and medication was assessed. Current medication use including medication on demand was recorded digitally by scanning the drug identification bar code from drug packages or alternatively established on the basis of self-reported information from participants (e.g., prescription plan). History of drug intake and the type of prescription (self-medication vs. prescription by a physician) were recorded for the medication. Central pharmaceutical numbers were translated into the Anatomical Therapeutic Chemical (ATC) code of the current pharmaceutical index. All study procedures were performed according to standard operating procedures. A central data management performed quality control with checks of all variables by pre-defined algorithms for completeness, plausibility, and validity.

Laboratory analyses

Measurements of humoral biomarkers were performed from blood samples of the study participants at the baseline visit, which were collected after a fasting period of at least 5 h. Concentration of humoral N-terminal pro-B-type natriuretic peptide (NT-proBNP; Elecysys proBNP II assay, ECLIA, Roche Diagnostics, Mannheim, Germany), cardiac troponin I (ACHITECT STAT highly sensitive Troponin I immunoassay, Abbott Diagnostic, USA, ARCHITECT i2000SR), C-reactive protein (CRP; Abbott Diagnostic, Wiesbaden, Germany), Apolipoprotein (Apo) A1, ApoB100 (Immunoturbidimetric method, Abbott Architect), and fibrinogen (Werfen Instrumentation Laboratory) were measured with commercially available assays directly after blood withdrawal. The estimated glomerular filtration rate (eGFR) was calculated by the MDRD formula [26].

Statistical analysis

Individuals were classified as VKA user or DOAC user according to ATC drug classification coding. Descriptive statistics (absolute numbers, frequencies for categorical values, medians with 25th and 75th percentile and means with corresponding standard deviation for continuous data) were generated for all dependent variables to compare treatment groups. Based on the literature, the following variables were selected for evaluating the effects of anticoagulant drugs on the cardiovascular system: cardiac structure (i.e., LV mass/height$^{2.7}$ and relative wall thickness), cardiac function (i.e., E/E' ratio and left ventricular ejection fraction), vascular function (i.e., stiffness index), humoral biomarkers of inflammation (i.e., fibrinogen and CRP), cardiac damage (i.e., NT-pro-BNP and troponin I), and lipid metabolism (i.e., ApoA1 and ApoB100). To take differences in clinical characteristics between groups as potential confounders into account, multivariate linear regression models with adjustment for age, sex, traditional cardiovascular risk factors, comorbidities, duration of intake of oral anticoagulants, and heart failure-related co-medication were calculated to compare the effects of DOAC and VKA (reference group) on the cardiovascular system. To evaluate a potential time-dependent effect of oral anticoagulation use on intermediate phenotypes of cardiovascular disease, the impact of history of VKA and DOAC treatment length was analyzed separately. In addition, propensity score-weighted analysis was performed to evaluate the robustness of results from regression analysis.

For a more homogeneous sample with regard to clinical characteristics, sensitivity analyses were conducted in study participants with atrial fibrillation and CHA_2DS_2–VASc score ≥ 1. Only participants with treatment duration of more than 3 months who received the diagnosis of atrial fibrillation after approval of DOACs by regulatory authorities (2011 for Germany), assuring that newly initiated anticoagulation therapy with DOAC was only applied to anticoagulation naïve subjects, were included in the analysis. A second sensitivity analysis was conducted in the subsample of subjects with asymptomatic heart failure (i.e., stage A according to the ACC/AHA heart failure classification) [27].

Statistical testing was performed with paired tests with post-hoc Bonferroni correction for multiple testing. Statistical analysis was conducted using the software program R, version 3.1.1 (http://www.r-project.org).

Results

Clinical characteristics of study participants

Clinical characteristics of the study sample are summarized in Table 1. The total sample comprised 404 VKA users and 229 DOAC users with a mean age of 68.8 ± 9.1 years and 68.2 ± 9.8 years, respectively. Among participants under DOAC treatment, $n = 159$ subjects received a factor Xa inhibitor and $n = 70$ a direct thrombin inhibitor. A detailed description of DOAC substances with corresponding dosages is presented in Table S1 in the Supplemental Material. Study participants with current VKA use had a higher stroke risk indicated by the CHA_2DS_2–VASc score. The risk profile of participants on VKA revealed a higher prevalence of traditional cardiovascular risk factors and clinical

Table 1 Clinical characteristics of study participants

	Individuals taking VKA ($N=404$)	Individuals taking DOAC ($N=229$)
Age (years)	68.8 ± 9.1	68.2 ± 9.8
Sex (female), % (n)	24.3 (98)	33.2 (76)
BMI (kg/m^2)	28.5 (25.6/31.6)	28.6 (25.4/32.0)
CHA_2DS_2–VASc score	3.55 ± 1.59	3.36 ± 1.69
eGFR (mL/min/1.73 m^2)[a]	66.1 ± 21.0	72.5 ± 17.6
Traditional cardiovascular risk factors, % (n)		
Diabetes mellitus	26.1 (105)	22.0 (50)
Dyslipidemia	62.2 (250)	55.5 (127)
Family history of myocardial infarction/stroke	21.6 (87)	21.4 (49)
Hypertension	81.4 (329)	79.5 (182)
Obesity	37.2 (149)	38.6 (88)
Smoking	10.5 (42)	9.6 (22)
Comorbidities, % (n)		
Chronic kidney failure	8.5 (33)	2.7 (6)
Congestive heart failure	64.6 (241)	53.9 (110)
Coronary artery disease	46.5 (186)	31.4 (71)
Deep vein thrombosis	2.0 (8)	6.2 (14)
Myocardial infarction	25.8 (103)	15.9 (36)
Peripheral artery disease	10.9 (43)	5.8 (13)
Pulmonary embolism	0.8 (3)	7.2 (16)
Stroke	13.8 (55)	12.3 (28)
Medication, % (n)[b]		
Agents acting on the renin–angiotensin system	35.9 (145)	45.9 (105)
Beta-blocking agents	35.6 (144)	48.5 (111)
Diuretics	28.2 (114)	31.0 (71)
Lipid-modifying agents	58.9 (238)	46.3 (106)

Data are expressed as relative and absolute frequencies for binary variables, for continuous variables as mean with standard deviation

[a]Calculated by MDRD formula [26]

[b]The following ATC codes were used for identification of concomitant intake of drugs: C09—agents acting on the renin–angiotensin system; C07—beta-blockers; C03—diuretics; C10—lipid-modifying agents

comorbidities (with the exception of deep vein thrombosis and pulmonary embolism) compared to DOAC users. The median international normalized ratio (INR) of the VKA group was 2.3 (IQR 2.1–2.8). Medical treatment of heart failure (i.e., agents interfering with the renin–angiotensin aldosterone system, beta-blockers, and diuretics) was more frequently applied to DOAC treated participants than to VKA users. Intake of anticoagulation for more than 1 year was present in 39.2% of subjects receiving DOAC, whereas it was recorded for 83.0% of individuals treated with VKA.

Comparison of functional and structural parameters and humoral biomarkers between VKA and DOAC therapy

Functional and structural parameters and humoral biomarkers of VKA and DOAC users are displayed in Table S2 in the Supplemental Material. In brief, univariate analysis revealed a significantly higher ApoA1 concentration, lower levels of troponin I and NT-pro-BNP, better cardiac function, and lower LV mass among DOAC users, whereas no differences were observed for ApoB100 levels and relative wall thickness.

Linear regression models adjusted for age, sex, cardiovascular risk factors, comorbidities, treatment duration, and co-medication were calculated to analyze the interrelation between intake of DOAC and echocardiographic parameters, stiffness index, and humoral biomarkers (Table 2). Differential relationships of DOAC compared to VKA therapy (reference) were found for E/E' ratio ($\beta=-0.24$ [95% CI −0.36; 0.12], $P=0.0001$), left ventricular mass ($\beta=-5.3$ [95% CI −10; −0.63], $P=0.027$), and ApoA1 ($\beta=0.11$ [95% CI 0.036; 0.18], $P=0.0038$). After correction for multiple testing according to

Table 2 Comparison of intermediate phenotypes of cardiovascular disease in individuals with DOAC and VKA therapy

	Crude model		Adjusted model[a]	
	β-estimate $_{\text{DOAC vs. VKA}}$ [95% CI]	*P* value	β-estimate $_{\text{DOAC vs. VKA}}$ [95% CI]	*P* value
HDL-cholesterol (mg/dL)	5.7 [3.2/8.1]	<**0.0001**	3.6 [−0.074/7.3]	0.055
ApoA1 (g/L)	0.15 [0.098/0.19]	<**0.0001**	0.11 [0.036/0.18]	**0.0038**
LDL cholesterol (mg/dL)	5.9 [−0.57/12.0]	0.074	8.9 [−0.73/19.0]	0.071
ApoB100 (g/L)	0.0037 [−0.039/0.046]	0.87	0.047 [−0.016/0.11]	0.14
CRP (mg/L)[b]	−0.17 [−0.33/−0.001]	0.049	0.11 [−0.15/0.37]	0.42
E/*E*′-ratio[b]	−0.25 [−0.33/−0.18]	<**0.0001**	−0.24 [−0.36/−0.12]	**0.0001**
Ejection fraction (%)	4.0 [2.1/5.9]	<**0.0001**	2.1 [−0.67/4.8]	0.14
Fibrinogen (mg/dL)	−24 [−39/−9.8]	**0.001**	−2.6 [−23/18]	0.80
LV mass/height$^{2.7}$ (g/m$^{2.7}$)	−5.1 [−8.1/−2.2]	<**0.0005**	−5.3 [−10/−0.63]	0.027
NT-pro-BNP (pg/mL)[b]	−0.48 [−0.68/−0.28]	<**0.0001**	3.1 [−1.4/7.7]	0.17
Relative wall thickness	−0.0008 [−0.02/0.02]	0.94	0.0057 [−0.025/0.036]	0.72
Stiffness index (m/s)	−0.55 [−1.1/0.004]	0.052	−0.41 [−1.3/0.44]	0.35
Troponin I (pg/mL)[b]	−0.30 [−0.48/−0.13]	<**0.0005**	0.083 [−0.17/0.34]	0.53

Effect estimates presented are β values for DOAC vs. VKA use derived from general linear models for each intermediate phenotype of cardiovascular disease (dependent variable)

P values passing the Bonferroni-corrected threshold of statistical significance (i.e., $P<0.004$) are indicated in bold print

ApoA1 apolipoprotein A1, *ApoB100* apolipoprotein B, *CRP* C-reactive protein, *LV* left ventricular, *NT-pro-BNP* N-terminal pro-B-type natriuretic peptide

[a]Adjusted for hypertension, diabetes, smoking, obesity, dyslipidemia, family history of myocardial infarction/stroke, history of myocardial infarction, coronary artery disease, asymptomatic cardiac dysfunction, symptomatic heart failure, peripheral artery disease, stroke, venous thromboembolism, eGFR, duration of treatment with oral anticoagulation therapy, lipid-lowering drugs, agents acting on the renin–angiotensin system, diuretics and beta-blocker

[b]Values were log transformed for regression analysis

Bonferroni's method, DOAC therapy was an independent significant predictor of better diastolic function (as indicated by the *E*/*E*′ ratio) and higher concentrations of ApoA1 compared to VKA therapy. Additional adjustment of DOAC dosages (low vs. high) did not change results (data not shown),

Propensity score-weighted analysis

Propensity score analysis with weighting for age, sex, cardiovascular risk factors, comorbidities, and intake of co-medication was undertaken to investigate the robustness of study results. After weighting, the two groups had well-balanced baseline characteristics (Table S3). Figure 1 and Table S4 display the absolute and relative median difference in the propensity score-weighted analysis between VKA and DOAC users regarding functional and structural cardiovascular parameters and humoral biomarkers. The largest relative difference between DOAC and VKA treated subjects was detected for *E*/*E*′ ratio (DOAC: 8.88 [6.62; 11.93] vs. VKA: 11.24 [8.19; 15.65]), followed by stiffness index (DOAC: 8.97 [7.31; 9.97] vs. VKA: 9.46 [7.92; 11.29] m/s), and ApoA1 concentration (DOAC: 1.63 [1.44; 1.80] vs. VKA: 1.57 [1.39; 1.84] g/L).

Sensitivity analyses

Sensitivity analyses were conducted to further evaluate the robustness of the previous findings (Table 3): the first sensitivity analysis was limited to participants with atrial fibrillation, a CHA_2DS_2–VASc score ≥ 1, diagnosis of atrial fibrillation in DOAC users after year 2011 and duration of oral anticoagulation treatment ≥ 3 months (Table S5). In multivariable linear regression analysis adjusted for potential confounders, the intake of DOACs was independently related to lower *E*/*E*′ ratio ($\beta=-0.24$ [95% CI −0.40; −0.068], $P=0.0064$), lower level of NT-pro-BNP ($\beta=-0.50$ [95% CI −0.86; −0.14], $P=0.0078$), increased HDL-cholesterol ($\beta=6.6$ [95% CI 1.4; 12.0], $P=0.014$) and higher level of ApoA1 ($\beta=0.18$ [95% CI 0.081; 0.28], $P=0.00052$) compared to the intake of VKA. No differences were detected for surrogate markers of arterial stiffness and systemic inflammation. In the second sensitivity, analysis of the subsample of individuals with asymptomatic heart failure (see Table S6 for clinical characteristics), linear regression analysis, yielded comparable results: in the fully adjusted regression models, DOAC use was related to a better diastolic function (*E*/*E*′ ratio: $\beta=-0.25$ [95% CI −0.39; −0.11], $P=0.00046$), higher ApoA1 ($\beta=0.095$ [95% CI 0.0011; 0.19], $P=0.049$). In

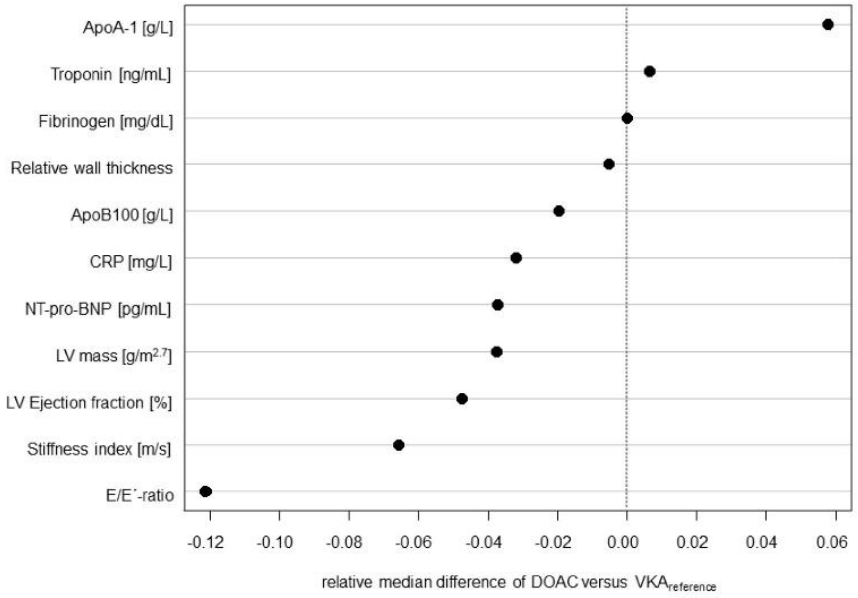

Fig. 1 Comparison of the profile of subclinical phenotypes of cardiovascular disease and inflammatory biomarkers in individuals with VKA and DOAC by propensity score-weighted analysis. Data are expressed as the relative median difference to the range between 5th and 95th percentiles. Variables are arranged in descending order of relative mean difference among the treatment groups. Variables considered for the propensity score model: sex, age, hypertension, diabetes, smoking, obesity, dyslipidemia, family history of myocardial infarction/stroke, history of myocardial infarction, stroke, asymptomatic cardiac dysfunction, symptomatic heart failure, coronary artery disease, peripheral artery disease, venous thromboembolism, eGFR, lipid-modifying drugs, diuretics, beta-blocker, and agents acting on the renin–angiotensin system. *ApoA1* apolipoprotein A1, *ApoB100* apolipoprotein B, *CRP* C-reactive protein, *LV* left ventricular, *NT-pro-BNP* N-terminal pro-B-type natriuretic peptide

addition, DOAC therapy was also linked to lower left ventricular mass ($\beta = -8.9$ [95% CI −15; −2.5], $P = 0.0069$) and a better left ventricular ejection fraction ($\beta = 4.8$ [95% CI 1.4; 8.3], $P = 0.0070$).

Relevance of history of oral anticoagulation treatment length

Since differences in the duration of treatment were observed between the DOAC and VKA sample, the duration of anticoagulation therapy was further analyzed. In regression analysis adjusted for age, sex, cardiovascular risk factors, comorbidities, and medication for heart failure, longer duration of VKA therapy was a predictor for worse diastolic function (*E*/*E*′: $\beta = 0.092$ [95% CI 0.055; 0.13], $P < 0.0001$), whereas longer DOAC treatment duration was not ($\beta = -0.034$ [95% CI −0.11; 0.042], $P = 0.38$). A similar result was found with regard to the levels of ApoA1: $\beta_{\text{VKA treatment duration}} = -0.034$ [95% CI −0.056; −0.012] ($P = 0.0032$) and $\beta_{\text{DOAC treatment duration}} = 0.0097$ [95% CI −0.038; 0.057] ($P = 0.69$).

Differences of IIa and Xa inhibition in comparison with VKA therapy

Finally, the traits *E*/*E*′ and ApoA1, which showed the strongest differences between anticoagulation groups, were exploratively investigated with regard to different target coagulation proteases of DOAC therapy. Figure 2 shows the regression estimates adjusted for age, sex, cardiovascular risk factors, comorbidities, treatment duration, and medication for the treatment of heart failure for *E*/*E*′ ratio and concentration of ApoA1 stratified by direct inhibition of factor Xa and IIa in comparison with VKA therapy. In comparison with VKA, Xa and IIa inhibitors showed no significant or clinically relevant difference in effects on *E*/*E*′ and ApoA1.

Discussion

This is the first comprehensive study in man to illustrate differential profiles for oral anticoagulants regarding cardiac structure and function as well as humoral biomarkers as intermediate phenotypes of cardiovascular disease. The

Table 3 Sensitivity analyses in pre-defined subgroups

	Individuals with atrial fibrillation[a] ($N=373$)		Individuals with asymptomatic heart failure[b] ($N=331$)	
	β-estimate $_{\text{DOAC vs. VKA}}$ [95% CI]	P value	β-estimate $_{\text{DOAC vs. VKA}}$ [95% CI]	P value
HDL-cholesterol (mg/dL)	6.6 [1.4/12.0]	0.014	4.0 [−0.71/8.6]	0.098
ApoA1 (g/L)	0.18 [0.081/0.28]	**0.00052**	0.095 [0.0011/0.19]	0.049
LDL cholesterol (mg/dL)	8.0 [−5.6/22]	0.25	−0.57 [−13/12]	0.93
ApoB100 (g/L)	0.040 [−0.046/0.13]	0.36	−0.014 [−0.095/0.066]	0.73
CRP (mg/L)[c]	0.021 [−0.33/0.37]	0.91	0.16 [−0.18/0.51]	0.35
E/*E*′-ratio[c]	−0.24 [−0.40/−0.068]	0.0064	−0.25 [−0.39/−0.11]	**0.00046**
Ejection fraction (%)	3.8 [−0.22/7.9]	0.066	4.8 [1.4/8.3]	0.0070
Fibrinogen (mg/dL)	−1.5 [−31/28]	0.92	−2.8 [−22/28]	0.82
LV mass/height$^{2.7}$ (g/m$^{2.7}$)	−4.6 [−11/1.7]	0.15	−8.9 [−15/−2.5]	0.0069
NT-pro-BNP (pg/mL)[c]	−0.50 [−0.86/−0.14]	0.0078	−0.32 [−0.67/−0.036]	0.080
Relative wall thickness	0.016 [−0.025/0.058]	0.44	0.057 [−0.033/0.044]	0.77
Stiffness index (m/s)	−0.43 [−1.8/0.90]	0.53	−0.28 [−1.4/0.84]	0.62
Troponin I (pg/mL)[c]	0.14 [−0.22/0.50]	0.46	−0.18 [−0.52/0.15]	0.27

Effect estimates presented are β values for DOAC vs. VKA use derived from general linear models for each intermediate phenotype of cardiovascular disease (dependent variable)

Adjusted for hypertension, diabetes, smoking, obesity, dyslipidemia, family history of myocardial infarction/stroke, history of myocardial infarction, coronary artery disease, asymptomatic cardiac dysfunction, symptomatic heart failure, peripheral artery disease, stroke, venous thromboembolism, eGFR, duration of treatment with oral anticoagulation therapy, lipid-lowering drugs, agents acting on the renin–angiotensin system, diuretics, and beta-blocker

P values passing the Bonferroni-corrected threshold of statistical significance (i.e., $P<0.004$) are indicated in bold print

ApoA1 apolipoprotein A1, *ApoB100* apolipoprotein B, *CRP* C-reactive protein, *LV* left ventricular, *NT-pro-BNP* N-terminal pro-B-type natriuretic peptide

[a]The sample was restricted to individuals with self-reported atrial fibrillation, CHA_2DS_2–VASc score ≥ 1, diagnosis of atrial fibrillation after year 2011 for DOAC users (excluding VKA-based anticoagulation therapy of AF prior to DOAC treatment) and a minimal duration of OAC treatment of 3 months

[b]Asymptomatic heart failure comprises individuals with stage A heart failure according to the ACC/AHA heart failure classification scheme

[c]Values were log transformed for regression analysis due to skewed distribution

empirical findings support evidence that specific anticoagulant agents interact with the development of cardiovascular disease in humans. DOAC-based anticoagulation therapy was an independent predictor of better cardiac diastolic function in comparison with VKA therapy. In addition, intake of DOAC was also related to higher concentration of ApoA1 providing novel insights into the interaction between anticoagulation therapy and lipid metabolism.

To date, experimental animal studies have linked the direct inhibition of factor Xa or thrombin by DOACs to attenuation of cardiac remodeling and improved cardiac function [13, 17–20, 28–30]. Azuma et al. have investigated the effect of rivaroxaban on atrial and ventricular remodeling in a sleep apnea mouse model presenting an attenuation of systolic function (ejection fraction: 51.8% vs. 55.8%) and diastolic function (*E*/*E*′: 29.4 vs. 24.6) [18]. Dong et al. showed a significantly improved myocardial function in dabigatran treated mice [13]. In line with these findings, the present results show differential effects of oral anticoagulants on myocardial function and structure in humans. A possible mechanism involves DOAC attenuated effects of factor Xa-induced activation of PAR-2 and PAR-1, or thrombin-induced activation of PAR-1, shown to induce hypertrophy of cultured cardiomyocytes and proliferation of cardiac fibroblasts [23, 31]. The role of these PAR-mediated effects was further demonstrated in cardiomyocyte-specific PAR-2 overexpressing transgenic mice, which had more extensive cardiac hypertrophy, fibrosis, inflammation, and heart failure, while PAR-2 deficiency attenuated cardiac remodeling and improved heart function after induced myocardial infarction [32]. Moreover, over-expression of PAR-1 on cardiomyocytes induced hypertrophy and dilated cardiomyopathy [33]. Although the use of VKA obviously also reduces levels of factor Xa and thrombin, potentially also diminishing PAR-mediated cellular effects, VKA inflict additional effects on the cardiovascular system. In part, these effects may be due to residual PAR activating properties of the so-called PIVKAs that may to some extend bind and activate PAR-1 or -2 [23, 34]. Furthermore, it is known that VKA inactivates Matrix Gla protein (MGP), a tissue calcification

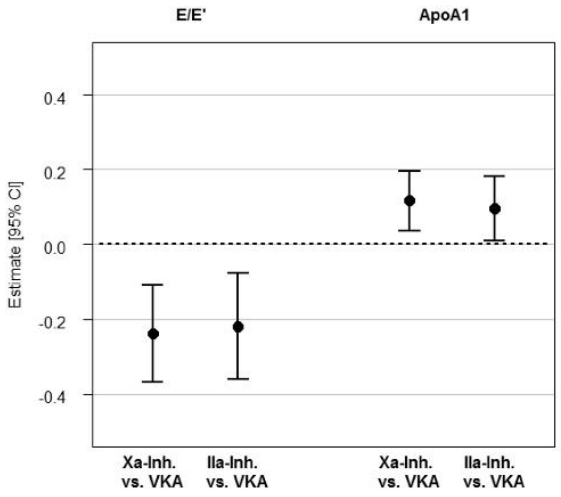

Fig. 2 Comparison of effect estimates of IIa and Xa-directed anticoagulation therapy compared to VKA therapy. The plots indicate the estimates IIa- and Xa-directed oral anticoagulation therapy on *E/E'* ratio and ApoA1 in comparison with VKA therapy. The effect estimates $_{\text{DOAC vs. VKA}}$ are adjusted for age, sex, cardiovascular risk factors, comorbidities, treatment duration, and medication for the treatment of heart failure. *ApoA1* apolipoprotein A1, *VKA* vitamin K antagonist

inhibitor, through its incomplete γ-carboxylation [21]. Evidence supporting effects of VKA on the development of aortic valve degeneration and calcification of soft tissues including aortic valve leaflets is found in the literature [35, 36]. These effects may also contribute to an impairment of cardiac function, although supporting evidence from human studies is still lacking.

The present study was the first to report differential links of DOAC and VKA with ApoA1 concentrations. In contrast, Jospeh et al. detected only small, non-significant changes in ApoA1 level among individuals on treatment with dabigatran. However, they reported a significant reduction of ApoB concentrations under treatment with dabigatran (−0.057 g/L for 110 mg dabigatran and −0.065 g/L for 150 mg dabigatran, respectively) [16]. It merits consideration that the current investigation was nested within a cohort study which was not limited to patients with atrial fibrillation (such as the RE-LY trial), but focused on individuals with heart failure, which might explain the findings. A possible mechanism for the altered lipoprotein metabolism might be the conversion of the prodrug dabigatran etexilate to dabigatran by microsomal carboxylesterase, which also regulates lipoprotein metabolism. The competing activity might also result in changes in ApoA1 concentrations [37, 38]. Alternatively, the observed differences of ApoA1 levels between DOAC and VKA therapy might also be—at least in part—attributable to potential negative effects of VKA on lipid metabolism. However, no experimental data are available that suggest an interplay between the effects of VKA therapy and lipid metabolism.

The current study adds to the raising body of literature that oral anticoagulants exhibit pleiotropic effects on the cardiovascular system, with potential impact on incident or prevalent cardiovascular disease; this is especially important when considering the widespread use of these drugs. The results are convincing, since interrelations remained robust in various subgroups analyses. DOACs were administered up to a maximum of 4 years in the present study sample, which is likely to underestimate the true effect of long-term therapy with these drugs as compared to VKA use. This is relevant for the interpretation of results, since parameters such as *E/E'*, LV ejection fraction, and NT-pro-BNP are of dynamic nature (and prone to early changes even after short time of exposure), whereas changes in structural parameters (e.g., left ventricular mass or relative wall thickness) are not comparably sensitive to short-term effects. In this context, it also merits consideration that a rather small effect size does not necessarily translate into small clinical relevance. For example, there is evidence available in the literature that an increase of ApoA-1 by 0.14 g/L (from 1.35 to 1.49 g/L) translates into a decreased odds ratio for stroke emphasizing a potential clinical relevance of such a small difference [39]. The differential findings on cardiac function raise the question whether this should affect clinical decision making regarding the choice of oral anticoagulants. Although adequately powered studies are needed to evaluate whether rather small differences in *E/E'* ratio between DOAC and VKA therapy translate into relevant differences in clinical outcome, the present study adds to the growing body of evidence that DOAC may exert beneficial effects on the onset and progression cardiovascular disease. Based on the limited evidence available at the moment, the clinical implications of the present study merit critical evaluation and call for future studies unraveling the mechanisms involved.

Strength and limitations

This is the first study in men, to comprehensively compare associations of DOAC and VKA therapy on intermediate phenotypes of cardiovascular disease and a laboratory panel of cardiovascular biomarkers. The key strengths of this study are the sample size and the detailed phenotyping in a highly standardized study setting (exceeding the setting of a clinical study). The evaluation of surrogate markers of intermediate disease phenotypes instead of clinical endpoints offers the opportunity to gain pathomechanistic insights in a biological continuum. Advanced statistical methods (i.e., multivariate regression analysis and propensity score weighting) and specific subgroup analyses were applied to address confounding and to confirm robustness and validity of results. However,

when interpreting the results, important limitations merit consideration: The findings of this study were derived in a study sample of individuals with heart failure and translation to other patient groups needs still to be demonstrated by future studies. The cross-sectional study design warrants for caution when interpreting the results with regard to causal inference. Due to the observational nature of the study, exposure has not been allocated randomly and limitations for retrospective studies might take effect. Although a large panel of potential confounders was used for adjustment in regression analysis, unmeasured confounders may still contribute to the observed differences. Information on genetic polymorphisms relevant for metabolism of oral anticoagulants (e.g., CYP2C9, VKORC1, and CES1) as well as the concentration of MGP and Gas-6 was not available for analysis in the present study. Finally, the study sample was not adequately powered to detect differences with regard to markers of subclinical cardiovascular disease between direct inhibitors of factor Xa and thrombin, respectively, in a head-to-head comparison.

Conclusion

The current study demonstrated that the modulation of the coagulation system by oral anticoagulants is differently linked to cardiac function as well as lipid metabolism. This supports the concept that specific oral anticoagulants exert distinct effects beyond their intended target of preventing the formation of clots. This novel and clinically manifest cross-link between anticoagulation therapy and cardiovascular disease merits critical attention, since it may have clinically relevant implications for individually tailored antithrombotic therapy.

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Author contributions PSW had full access of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Conception and study design: LE, JHP, and PSW. Substantial contribution to acquisition, analysis, or interpretation of data: all authors. Data management and statistical analysis: AS, LE, JHP, and PSW. Drafting the manuscript: LE, JHP, and PSW. Revising manuscript critically for important intellectual content: all authors. Final approval of the version to be published: all authors.

Compliance with ethical standards

Conflict of interest P.S.W., M.P.N., and J.H.P. are funded by the Federal Ministry of Education and Research (BMBF 01EO1503). P.S.W. has received research funding from Boehringer Ingelheim; PHILIPS Medical Systems; Sanofi-Aventis; Bayer Vital; Daiichi Sankyo Europe; Federal Institute for Occupational Safety and Health (BAuA); Initiative 'Health Economy', Ministry of Health and Ministry of Economics, Rhineland-Palatinate; Federal Ministry of Education and Research; Federal Ministry of Health, Rhineland-Palatinate (MSAGD); Mainz Heart Foundation; EU Grant agreement no. 278913, 278397 and received honoraria for lectures or consulting from Boehringer Ingelheim, Bayer HealthCare, Evonik, AstraZenca and Sanofi-Aventis.

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SUPPLEMENTAL MATERIAL

Direct oral anticoagulants and vitamin K-antagonists are linked to differential profiles of cardiac function and lipid metabolism

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DETAILED METHODS

Definition of traditional cardiovascular risk factors

Cardiovascular risk factors were defined as follows: smoking was dichotomized into nonsmokers (never and ex-smokers) and smokers (occasional and current smoker). Obesity was defined as a body mass index (BMI) ≥ 30 kg/m². Diabetes was defined as a definite diagnosis of diabetes by a physician, current intake of antidiabetic drugs, or HbA1c ≥6.5 Dyslipidemia was defined as a diagnosis by a physician, current intake of lipid-lowering drugs, or a low-density lipoprotein/ high-density lipoprotein ratio of >3.5. Hypertension was diagnosed, if antihypertensive drugs were taken, or if the mean systolic blood pressure was ≥ 140 mm Hg (diastolic ≥ 90 mm Hg) in the 2nd and 3rd standardized measurement after 8 and 11 min of rest. A positive family history of MI was defined as at least one MI in a female first-degree relative of < 65 years or a male first-degree relative of < 60 years.

SUPPLEMENTAL TABLES

Supplemental Table 1. DOAC substances with corresponding dosages

	N
Dabigatran (B01AE07)	
75 mg	3
110 mg	34
150 mg	33
Rivaroxaban (B01AF01)	
10 mg	4
15 mg	15
20 mg	95
Apixaban (B01AF02)	
2,5 mg	7
5,0 mg	35

Supplemental Table S2. Univariate comparison of VKA and DOAC treated subject regarding parameters

	Individuals taking VKA (N=404)	Individuals taking DOAC (N=229)	p value
ApoA1 [g/L]	1.51±0.29	1.65±0.30	< 0.0001
ApoB100 [g/L]	0.96±0.26	0.96±0.26	0.86
CRP [mg/L]	2.60 (1.40/5.50)	2.20 (1.10/4.70)	0.031
E/E´-ratio	11.08 (8.13/16.12)	8.88 (6.65/12.01)	< 0.0001
Ejection fraction [%]	47.3±12.4	51.3±10.8	< 0.0001
Fibrinogen [mg/dL]	358 (310/426)	340 (292/392)	0.0027
LV mass/ height$^{2.7}$ [g/m$^{2.7}$]	51.7 (42.0/64.9)	46.9 (37.5/58.0)	< 0.0005
NT-pro-BNP [pg/mL]	760.0 (315.0/1577.0)	437.0 (184.0/1101.0)	< 0.0001
Relative wall thickness	0.40 (0.34/0.49)	0.40 (0.34/0.50)	0.89
Stiffness index [m/s]	9.53±2.44	8.98±2.34	0.05
Troponin I [pg/mL]	7.60 (4.20/17.26)	5.80 (3.00/10.97)	0.00029

Supplemental Table S3. Clinical characteristics of study participants after propensity score weighting.

	Individuals taking VKA (N=208)	Individuals taking DOAC (N=96)
Age [years]	68.2±9.2	68.1±9.8
Sex (Female), % (n)	37.0% (77)	33.0% (69)
BMI [kg/m^2]	28.6±5.4	29.0±4.8
CHA_2DS_2-VASc score	3.38±1.60	3.34±1.67
eGFR [ml/min/1.73m^2] *	72.16±18.75	72.07±17.48
Traditional cardiovascular risk factors, % (n)		
Diabetes mellitus	19.4% (40)	21.5% (45)
Dyslipidemia	50.4% (105)	54.5% (114)
Family history of myocardial infarction /stroke	19.9% (41)	20.6% (43)
Hypertension	80.1% (167)	78.9% (165)
Obesity	34.3% (71)	36.8% (77)
Smoking	9.0% (19)	9.1% (19)
Comorbidities, % (n)		
Chronic kidney failure	5.2% (11)	2.9% (6)
Congestive heart failure	55.8% (107)	54.5% (103)
Coronary artery disease	29.9% (62)	30.6% (64)
Deep vein thrombosis	3.5% (7)	6.2% (13)
Myocardial infarction	14.3% (30)	15.3% (32)
Peripheral artery disease	5.6% (12)	5.7% (12)
Pulmonary embolism	3.6% (7)	7.2% (15)
Stroke	12.7% (26)	12.0% (25)
Co-medication use, % (n) ‡		
Agents acting on the renin-angiotensin system	44.6% (93)	45.5% (95)
Beta blocking agents	51.4% (107)	49.3% (103)
Diuretics	31.1% (65)	31.1% (65)
Lipid-modifying agents	26.8% (56)	28.7% (60)

The following variables were considered for propensity score-weighting: sex, age, hypertension, diabetes, smoking, obesity, dyslipidemia, family history of myocardial infarction/stroke, history of myocardial infarction, stroke, asymptomatic cardiac dysfunction, symptomatic heart failure, coronary artery disease, peripheral artery disease, venous thromboembolism, eGFR, lipid-modifying drugs, diuretics, beta-blocker, agents acting on the renin-angiotensin system. * calculated by MDRD formula.

Supplemental Table S4. Comparison of the effects of VKA and DOAC therapy in propensity score weighted analysis.

	Individuals receiving VKA (N= 208)	Individuals receiving DOAC (N=209)	Difference of medians (DOAC versus VKA)
ApoA1 [g/L]	1.57	1.63	0.06
ApoB100 [g/L]	0.956	0.94	-0.016
CRP [mg/L] [a]	2.50	2.10	-0.40
E/E´-ratio [a]	11.2	8.88	-2.36
Ejection fraction [%]	54.3	52.5	-1.73
Fibrinogen [mg/dL] [a]	340	340	0
LV mass/ height$^{2.7}$ [g/m$^{2.7}$]	48.9	47.0	-1.98
NT-pro-BNP [pg/mL] [a]	570	431	-139
Relative wall thickness	0.401	0.39	-0.002
Stiffness index [m/s]	9.46	8.97	-0.497
Troponin I [pg/mL] [a]	5.52	5.85	0.329

The following variables were considered for propensity score-weighting: sex, age, hypertension, diabetes, smoking, obesity, dyslipidemia, family history of myocardial infarction/stroke, history of myocardial infarction, stroke, asymptomatic cardiac dysfunction, symptomatic heart failure, coronary artery disease, peripheral artery disease, venous thromboembolism, eGFR, lipid-modifying drugs, diuretics, beta-blocker, agents acting on the renin-angiotensin system.
[a] values were log transformed for regression analysis
ApoA1, Apolipoprotein A1; ApoB100, Apolipoprotein B; CRP, C-reactive protein; LV, left ventricular; NT-pro-BNP, N-terminal pro-B-type natriuretic peptide

Supplemental Table S5. Clinical characteristics of AF subgroup (n=373)*

	Individuals taking VKA (N=277)	Individuals taking DOAC (N=96)
Age [years]	70.1±8.1	69.3±9.0
Sex (Female), % (n)	28.2 (78)	31.2 (30)
BMI [kg/m^2]	29.1±5.0	29.1±5.0
CHA_2DS_2-VASc score	3.70±1.53	3.44±1.55
eGFR [ml/min/1.73m^2] †	63.79±20.35	70.03±17.88
Traditional cardiovascular risk factors, % (n)		
Diabetes mellitus	28.6 (79)	27.4 (26)
Dyslipidemia	62.0 (171)	49.0 (47)
Family history of myocardial infarction /stroke	21.7 (60)	20.8 (20)
Hypertension	83.0 (230)	83.3 (80)
Obesity	36.0 (99)	37.5 (36)
Smoking	8.8 (24)	10.5 (10)
Comorbidities, % (n)		
Chronic kidney failure	11.2 (30)	4.2 (4)
Congestive heart failure	71.3 (179)	55.8 (48)
Coronary artery disease	43.1 (119)	37.9 (36)
Deep vein thrombosis	1.1 (3)	0 (0)
Myocardial infarction	23.0 (63)	23.0 (63)
Peripheral artery disease	8.9 (24)	7.4 (7)
Pulmonary embolism	0.4 (1)	2.1 (2)
Stroke	12.0 (33)	12.5 (12)
Co-medication use, % (n) ‡		
Agents acting on the renin-angiotensin system	35.7 (99)	54.2 (52)
Beta blocking agents	36.8 (102)	52.1 (50)
Diuretics	31.4 (87)	33.3 (32)
Lipid-modifying agents	22.0 (61)	31.2 (30)

*The sample was restricted to individuals with self-reported atrial fibrillation, CHA2DS2-VASc -Score ≥1, diagnosis of atrial fibrillation after year 2011 for DOAC users (excluding VKA-based anticoagulation therapy of AF prior to DOAC treatment) and a minimal duration of OAC treatment of 3 months;
† calculated by MDRD formula;
‡ ATC-Codes: agents acting on the renin-angiotensin system C09; beta blocking agents C07; diuretics C03; lipid-modifying agents C10.

Supplemental Table S6. Clinical characteristics of subjects with asymptomatic heart failure (according to AHA classification level B (n=331)

	Individuals taking VKA (N=199)	Individuals taking DOAC (N=132)
Age [years]	67.7±9.1	67.6±10.0
Sex (Female), % (n)	20.6 (41)	22.7 (30)
BMI [kg/m^2]	27.6 (25.1/30.4)	28.0 (25.0/31.0)
CHA_2DS_2-VASc score	3.15±1.56	3.02±1.69
eGFR [ml/min/1.73m^2] †	69.45±19.34	73.93±17.63
Traditional cardiovascular risk factors, % (n)		
Diabetes mellitus	19.2 (38)	21.5 (28)
Dyslipidemia	60.4 (119)	57.6 (76)
Family history of myocardial infarction /stroke	20.6 (41)	21.2 (28)
Hypertension	80.4 (160)	74.2 (98)
Obesity	74.2 (98)	33.3 (44)
Smoking	12.3 (24)	9.2 (12)
Comorbidities, % (n)		
Chronic kidney failure	5.1 (10)	1.5 (2)
Congestive heart failure	54.4 (98)	45.9 (56)
Coronary artery disease	41.9 (83)	30.8 (40)
Deep vein thrombosis	1.5 (3)	8.4 (11)
Myocardial infarction	17.7 (35)	13.8 (18)
Peripheral artery disease	8.2 (16)	3.9 (5)
Pulmonary embolism	1.0 (2)	8.4 (11)
Stroke	14.6 (29)	9.2 (12)
Co-medication use, % (n) ‡		
Agents acting on the renin-angiotensin system	34.2 (68)	47.0 (62)
Beta blocking agents	34.7 (69)	49.2 (65)
Diuretics	21.6 (43)	26.5 (35)
Lipid-modifying agents	25.1 (50)	32.6 (43)

† calculated by MDRD formula;
‡ ATC-Codes: agents acting on the renin-angiotensin system C09; beta blocking agents C07; diuretics C03; lipid-modifying agents C10.

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Thieme

Einschätzung von Ärzten zur medizinischen Versorgung mit oralen Antikoagulanzien

Physicians' Opinion on Health Care in Oral Anticoagulation

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Schlüsselwörter
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Key words
oral anticoagulation therapy, health care research, vitamin K-antagonists, direct oral anticoagulants

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ZUSAMMENFASSUNG

Hintergrund Mit der Einführung der direkten oralen Antikoagulanzien (DOAK) hat das Gebiet der antithrombotischen Therapie eine zunehmende Komplexität erfahren, da neben den etablierten Vitamin-K-Antagonisten (VKA) nun zahlreiche Therapiealternativen zur Verfügung stehen. Untersuchungen zur ärztlichen Bewertung der derzeitigen Behandlungssituation, welche für die Weiterentwicklung von Behandlungsstrategien neben Studien zur Pharmakovigilanz von großer Bedeutung sind, finden sich in der Literatur kaum.

Methoden Es wurden 11 700 praktizierende Ärzte in Rheinland-Pfalz zur Teilnahme an der webbasierten Befragung „Medizinische Versorgung mit oralen Antikoagulanzien (OAK)" kontaktiert. Nach detaillierter Qualitätskontrolle wurden die ärztlichen Angaben der thrombEVAL-Ärztebefragung in Zusammenschau mit Versorgungsforschungsdaten zu VKA-Patienten des thrombEVAL-Studienprogramms (N = 2011) analysiert.

Ergebnisse Insgesamt nahmen 512 Ärzte (durchschnittliches Alter: 48,0 ± 9,6 Jahre; 74,0 % männlich) an der Studie teil. Die Versorgungsqualität mit OAK wurde mit „befriedigend" (2,9 ± 0,9) bewertet. Im Vergleich zur medizinischen Regelversorgung zeigten die ärztlichen Angaben Abweichungen hinsichtlich der Einschätzung der Zeit im therapeutischen Bereich (+ 6,4 % [95 %-KI 2,7 %; 9,5 %]), der Länge der Kontrollabstände (– 35,0 % [28,0 %; 41,4 %]) sowie der OAK-bedingten Komplikationen (+ 61,8 % [37,8 %; 83,3 %]), deren Ausmaß in Facharztgruppen spezifische, statistisch-signifikante Unterschiede aufwies. Die Bereitschaft DOAK einzusetzen war bei Hausärzten ca. 50 % geringer als bei fachärztlich tätigen Ärzten (36,6 % [25,4 %; 47,8 %] vs. 72,4 % [66,0 %; 78,9 %]; p < 0,0001). Hinsichtlich des Managements der OAK-Therapie befürworteten 73,8 % (69,7 %; 77,9 %) die Einrichtung einer Beratungshotline sowie 67,3 % (62,9 %; 71,6 %) einen spezialisierten Gerinnungsdienst.

Diskussion Die vorliegende Ärztebefragung weist darauf hin, dass auf dem Gebiet der OAK-Therapie ein Optimierungsbedarf besteht. Die optimierte Therapie mit DOAK und VKA mit zusätzlicher Unterstützung durch spezialisierte Versorgungsangebote könnte zur Verbesserung der aktuellen Versorgungslage beitragen.

* Die Autoren haben in gleichem Anteil zur vorliegenden Arbeit beigetragen und sind als Erstautor/in des vorliegenden Artikels anzusehen.

ABSTRACT

Background The introduction of direct oral anticoagulants (DOAC) in addition to the established Vitamin K antagonist (VKA) has increased the complexity of antithrombotic therapy leading to numerous treatment options. Studies of the medical evaluation of the current treatment situation by health care providers, which are of great importance for the development of treatment strategies in addition to studies on pharmacovigilance, are limited in the literature.

Methods 11 700 physicians (Rhineland-Palatinate, Germany) were contacted to participate in the web-based survey on health care with oral anticoagulation (OAC). After detailed quality control, the study was analysed in synopsis with routine care data of VKA patients of the thrombEVAL study programme (N = 2.011).

Results In total, 512 physicians (mean age: 48.0 ± 9.6 years; 74.0 % male) participated in the study. In general, quality of OAC therapy was rated as "average/satisfactory" (2.9 ± 0.9). Comparison of physicians' perception with data from routine care highlighted marked differences regarding time in therapeutic range (+ 6.4 % [95 %-CI 2.7 %; 9.5 %]), duration of control intervals (– 35.0 % [28.0 %; 41.4 %]) and rate of OAC-related complications (+ 61.8 [37.8 %; 83.3 %], which differed additionally and statistically-significant between physician groups. The willingness to use DOAC was approximately 50 % lower in general physicians as compared to specialists (36.6 % [25.4 %; 47.8 %] vs. 72.4 % [66.0 %; 78.9 %]; p < 0.0001). Regarding management of OAC therapy, 73.8 % [69.7 %; 77.9 %] advocated the establishment of a service hotline and 67.3 % [62,9 %; 71.6 %] a specialized coagulation service.

Discussion The present survey among physicians reveals a need for optimization of OAC therapy in daily practice. Specialized care models might facilitate optimized OAC therapy with both VKAs and DOACs.

Um die Lesbarkeit des Artikels zu erleichtern, wurde durchgängig für alle Personen die grammatikalisch männliche Form verwendet. Diese Schreibweise dient der Vereinfachung und beinhaltet keine Diskriminierung anderer Geschlechtsformen.

Hintergrund

Aktuell werden in Deutschland ca. 1,6 Millionen Patienten mit oralen Antikoagulanzien (OAK) zur Primär- und Sekundärprävention thromboembolischer Ereignisse behandelt [1]. Seit Jahrzehnten sind Vitamin-K-Antagonisten (VKA) in der pharmakologischen Behandlung von Patienten mit Indikation zur OAK etabliert. Seit 2008 stehen zusätzlich neue, direkte orale Antikoagulanzien (DOAK) für spezifische Indikationen alternativ zur Verfügung. Aufgrund des demografischen Wandels, der steigenden Lebenserwartung, aber auch infolge der Ausweitung des Indikationsgebiets der Therapie mit OAK bei Patienten mit Vorhofflimmern, wird in den kommenden Jahren ein weiterer Anstieg der Patientenzahlen erwartet [1]. Diese Faktoren, aber auch die verbesserte Behandlung von Herz-Kreislauferkrankungen tragen zu einer zunehmenden Multimorbidität älterer Menschen bei [2]. Die aktuell noch limitierte wissenschaftliche Evidenz bezüglich des Therapie-Managements mit DOAK im klinischen Alltag sowie die zunehmende Multimorbidität vieler Patienten führen zu einer erhöhten Komplexität der Therapie mit OAK. Aktuelle Studien lassen vermuten, dass auch die Blockade von Faktor XI und XII eine attraktive Strategie zur Antikoagulation bietet [3]. Außerdem besteht bei vielen Patienten mit Indikation zur therapeutischen Antikoagulation eine relevante Unterversorgung mit OAK, welche unterschiedliche Ursachen hat (z. B. stattgehabte Blutungsereignisse oder erhöhtes Sturzrisiko) [4]. Eine Vielzahl von Studien untersucht derzeit den Nutzen von VKA sowie DOAK hinsichtlich Wirksamkeit, Sicherheit und gesundheitsökonomischer Effektivität, allerdings wurde bis dato keine Evaluation des ärztlichen Meinungsbildes zur derzeitigen Behandlungssituation und Therapieoptionen mit OAK durchgeführt.

Das Centrum für Hämostase und Thrombose an der Universitätsmedizin Mainz wird als integriertes Forschungs- und Behandlungszentrum des Bundesministeriums für Bildung und Forschung gefördert und hat den Auftrag und das Ziel, die Behandlung von Patienten mit OAK wissenschaftlich zu untersuchen und Ansätze für eine Verbesserung der medizinischen Versorgung zu identifizieren [5]. Vor diesem Hintergrund wird seit 2011 das Studienprogramm thrombEVAL unter der Schirmherrschaft der Landesregierung Rheinland-Pfalz am Centrum für Hämostase und Thrombose durchgeführt [6].

Ziel der vorliegenden Arbeit war es, eine Einschätzung der aktuellen medizinischen Versorgung mit OAK sowie der ärztlichen Aus- und Weiterbildung auf dem Gebiet von Ärztinnen und Ärzten in einer Befragung zu erheben und ihre Bewertung der Möglichkeiten zur Optimierung der bestehenden Versorgung von antikoagulierten Patienten zu erfassen.

Methoden

Studiendesign

Das thrombEVAL-Studienprogramm untersucht die Therapiequalität mit OAK in der medizinischen Regelversorgung sowie deren Optimierungsmöglichkeiten. Im Rahmen des thrombEVAL-Studienprogramms erfolgte eine Stakeholder-Analyse, anhand derer die Bewertung der aktuellen Versorgung mit OAK durch beruflich tätige Ärzte per Online-Befragung evaluiert wurde. Die ausführliche Darstellung des Studiendesigns der thrombEVAL-Studie sowie erste Auswertungsergebnisse zur Qualität der Therapie mit OAK wurden bereits veröffentlicht [6 – 8]. Die Studienkoordination und -durchführung, Datenmanagement und statistische Auswertung erfolgten durch das Centrum für Hämostase und Thrombose. Vor Studieninitiierung wurde ein positives Votum der Ethik-

kommission der Landesärztekammer Rheinland-Pfalz (Referenznummer 837.407.10.7415/7416) sowie der Datenschutzbeauftragten der Universitätsmedizin Mainz eingeholt. Zur Qualitätssicherung und Kontrolle der Datenerhebung erfolgte ein Studienmonitoring durch ein unabhängiges Institut (IZKS Mainz).

Datenerhebung

Für die Analyse wurden ca. 11 700 praktizierende Ärzte aller medizinischer Fachrichtungen in Rheinland-Pfalz im Jahr 2014 zur Teilnahme an einer Umfrage zum Thema „Medizinische Versorgung mit OAK" schriftlich eingeladen. Die Umfrage erfolgte anonym über eine webbasierte elektronische Befragung mit vordefinierten Pflichtfeldern, Filterfragen und Plausibilitätskontrollen. Die Fragen beinhalteten Formate mit vordefinierten Items (Multiple Choice), sechsstufigen Skalen vom Likert-Typ („sehr gut" bis „ungenügend") sowie offenen Antwortmöglichkeiten. Die Online-Befragung enthielt insgesamt 37 Fragen zu folgenden OAK-spezifischen Themen:

- Komplexität der klinischen Hämostaseologie
- Qualität der aktuellen Versorgung, Beurteilung des eigenen Wissens und der eigenen Fähigkeiten
- Bedarf an Angeboten zur Subspezialisierung im Rahmen der ärztlichen Weiterbildung
- neue Versorgungsformen (z. B. 24h-Beratungshotline, spezialisierter Gerinnungsdienst)
- neue, direkte Antikoagulanzien
- Herausforderungen und Versorgungslücken im klinischen Alltag
- arztbezogene Daten (Alter, Geschlecht, Arztbezeichnung, berufliche Stellung und Berufserfahrung)

Statistische Auswertung

Für die Darstellung kontinuierlicher Daten wurde in Abhängigkeit von der Schiefe der Daten entweder ein t-test für ungleiche Varianzen mit Satterthwaite Korrektur der Freiheitsgrade oder ein Wilcoxon- bzw. Mann-Whitney-Test verwendet, für kategoriale Daten ein exakter Test nach Fisher. Für die deskriptive Auswertung wurden absolute und relative Häufigkeiten berechnet. Die Selbsteinschätzung des eigenen Fachwissens (Skala: sehr gut bis ungenügend) im jeweiligen Fachgebiet wurde als Mittelwert mit zugehöriger Standardabweichung bestimmt. Die Ergebnisse dieser Umfrage wurden mit Versorgungsdaten der Kohorte der medizinischen Regelversorgung des thrombEVAL-Studienprogramms (N = 2011 Patienten mit Vitamin-K-Antagonisten, die zwischen Januar 2011 und März 2013 in das thrombEVAL-Studienprogramm eingeschlossen wurden) bezüglich der Qualität der Antikoagulationstherapie, der Abstände der INR-Kontrollen und der Komplikationsraten vergleichend analysiert. Für alle Daten erfolgte eine standardisierte und detaillierte Qualitätskontrolle anhand definierter Plausibilitätskriterien. Die Berechnung der Zeit im therapeutischen Bereich („time in therapeutic range", TTR) – ein Surrogatparameter für die Qualität der VKA-Therapie – erfolgte anhand der linearen Interpolationsmethode [9]. Die Häufigkeiten von Komplikationen in der Kohorte der medizinischen Regelversorgung wurden über einen Zeitraum von 12 Monaten nach Studieneinschluss ausgewertet. Signifikanztestungen wurden ausschließlich zu explorativen Zwecken durchgeführt. Die statistische Auswertung erfolgte mit der Software des R-Projekts (Version 3.2.2; http://www.r-project.org).

Ergebnisse

Von insgesamt 11 700 kontaktierten, berufstätigen Ärzten nahmen 512 (Rücklaufquote 4,4 %) an der Onlinebefragung teil. Das mittlere Alter der Teilnehmer betrug 48 ± 9,6 Jahre und die Mehrheit der Teilnehmer war männlich (74,0 %). Die Charakteristika der teilnehmenden Ärzte sind in ▶ **Tab. 1** dargestellt. Die teilnehmenden Ärzte waren in nahezu gleichen Anteilen im stationären und ambulanten Bereich tätig. Das Kollektiv umfasste 14,8 % hausärztlich, 39,7 % fachärztlich tätige Ärzte bzw. Ärzte in Weiterbildung und 45,5 % Ärzte, die keine OAK-Therapie durchführten. Die Mehrheit befand sich zum Zeitpunkt der Umfrage nicht mehr in einer Facharztweiterbildung (90,4 %). In der Gruppe der Ärzte, die keine OAK-Therapie durchführten, stellten Zahnmediziner den größten Anteil dar (32,6 %). Bezogen auf das Gesamtkollektiv gab ca. die Hälfte aller Ärzte an, über eine Berufserfahrung von mehr als 20 Jahren zu verfügen.

Ärztliche Weiterbildung und Einschätzung des allgemeinen und eigenen Fachwissens

In ▶ **Tab. 2** sind die Einschätzungen zum Fach Hämostaseologie dargestellt. Ca. 50 % aller Teilnehmer gaben eine starke Zunahme der Komplexität des Faches an. Die Notwendigkeit zur Spezialisierung im Bereich Hämostaseologie wurde von nicht-hausärztlich tätigen Ärzten nahezu doppelt so hoch eingeschätzt als von hausärztlich tätigen Ärzten. Unabhängig von der zugrundeliegenden Fachdisziplin sprach sich eine Mehrheit (56,0 % [95 %-KI 51,5 %; 60,6 %]) der Befragten gegen die Einrichtung einer Weiterbildung zum Facharzt für Hämostaseologie aus.

Die Versorgungsqualität mit OAK bewerteten die befragten Ärzte im Durchschnitt mit der Note 2,9 ± 0,9 und somit als befriedigend, wobei geringe Unterschiede zwischen fachärztlich tätigen und hausärztlich tätigen Ärzten zu verzeichnen waren (fachärztlich tätig: 3,0 ± 0,9 vs. hausärztlich tätig: 2,6 ± 0,9; $p < 0{,}001$). Der Patientenanteil, der bei bestehender Indikation eine entsprechende OAK-Therapie erhielt, wurde andererseits mit nur 15 % (Interquartilsabstand [IQA] 5 %/50 %) eingeschätzt. Der geschätzte Anteil an Patienten mit OAK-Therapie, bei denen eine medizinisch relevante Compliance-Störung vorlag, lag bei 15 % (IQA 5 %/25 %). Bei der Selbsteinschätzung des eigenen Wissens auf dem Gebiet der OAK-Therapie stellten sich Unterschiede zwischen den Fachgruppen dar: 29,6 % (18,9 %; 40,2 %) der hausärztlich tätigen Ärzten schätzten ihr Wissen mit den Noten „sehr gut" oder „gut" ein, wohingegen der Anteil bei den fachärztlich tätigen Ärzten bei 42,7 % (35,6 %; 49,8 %) lag. Ärzte, die keine Therapie mit OAK unmittelbar betreuen, ordneten ihr eigenes Wissen überwiegend in die Kategorien „befriedigend" und „ausreichend" ein (▶ **Abb. 1**).

Bewertung der Qualität der OAK-Therapie

Das ärztliche Meinungsbild zeigte sich sehr heterogen bezüglich der Einschätzung der Zeit, die sich Patienten unter der VKA-Therapie im therapeutischen Zielbereich befinden: Hausärztlich täti-

▶ **Tab. 1** Merkmale der Teilnehmer an der Erhebung (n = 512).

Merkmal	Häufigkeit
Alter, Jahre	48,0 ± 9,6
Geschlecht (männlich), %	74,0
Tätigkeitsbereich	
▪ Klinik, % (n)	52,1 (267)
▪ nicht universitäres Krankenhaus	64,1 (171)
▪ Universitätsklinik	29,6 (79)
▪ Reha-Klinik	6,4 (17)
▪ Niederlassung, % (n)	46,5 (238)
▪ medizinisches Versorgungszentrum, % (n)	1,0 (5)
▪ sonstiger medizinischer Bereich, % (n)	0,4 (2)
Arztbezeichnung	
▪ hausärztlich tätig, % (n)	14,5 (74)
▪ Allgemeinmediziner	77,0 (57)
▪ hausärztlich tätiger Internist	21,6 (16)
▪ Praktischer Arzt	1,4 (1)
▪ fachärztlich tätig, % (n)	75,5 (387)
▪ Anästhesiologie	8,8 (34)
▪ Chirurgie	17,6 (68)
▪ Innere Medizin	24,5 (95)
▪ Neurologie	5,2 (20)
▪ Zahnmedizin	23,0 (89)
▪ sonstige	20,9 (81)
▪ in Weiterbildung, % (n)	9,6 (49)
▪ Anästhesiologie	18,4 (9)
▪ Chirurgie	12,2 (6)
▪ Innere Medizin	53,0 (26)
▪ sonstige	16,3 (8)
▪ sonstige Arztbezeichnung, % (n)[1]	0,4 (2)
Erfahrung im ärztlichen Beruf	
▪ Berufserfahrung, % (n)	
▪ < 5 Jahre	6,8 (35)
▪ 5 – 10 Jahre	12,1 (62)
▪ 11 – 20 Jahre	29,5 (151)
▪ > 20 Jahre	51,6 (264)
▪ Erfahrung mit oraler Antikoagulationstherapie, % (n)	
▪ Keine Betreuung	13,9 (71)
▪ < 5 Jahre	9,4 (48)
▪ 5 – 10 Jahre	12,3 (63)
▪ 11 – 20 Jahre	27,9 (143)
▪ > 20 Jahre	36,5 (187)

[1] Ärzte, die im akademischen Bereich arbeiten, ohne direkten Patientenkontakt

ge Ärzte schätzten die TTR der Patienten unter OAK-Therapie um 5,5 % höher ein als die befragten Internisten (77,1 ± 18,1 % vs. 71,6 ± 11,1 %; p = 0,029). Es zeigte sich eine positive Korrelation (Pearson-Korrelationskoeffizient r = 0,14) zwischen Berufserfahrung und Einschätzung der Größe der TTR (p = 0,028). Der Vergleich der ärztlichen Angaben zur Therapiequalität mit TTR-Messungen in der medizinischen Regelversorgung ergab, dass die von befragten hausärztlich tätigen Ärzten angegebene TTR um 11,3 Prozentpunkte (6,7; 15,8) höher lag als die berechnete TTR von Patienten der medizinischen Regelversorgung, die durch hausärztlich tätige Ärzte betreut wurden (77,1 ± 18,1 % vs. 65,8 ± 24,6 %). Bei fachärztlich tätigen Internisten lag diese Differenz zwischen Einschätzung und tatsächlich gemessener TTR bei 2,0 Prozentpunkten (1,4; 5,5) (▶ **Tab. 3**). Im Gegensatz zu den Daten der Regelversorgung, bei denen eine höhere TTR bei internistisch-betreuten Patienten zu verzeichnen war, zeigten sich bei den Angaben zur Selbsteinschätzung höhere TTR-Werte bei hausärztlich tätigen Ärzten im Vergleich zu fachärztlich tätigen Internisten (77,1 % [72,8 %; 81,3 %] vs. 71,6 % [69,2 %; 74,1 %]).

Die durchschnittlichen Zeitabstände zwischen den Kontrolluntersuchungen mit INR-Bestimmung wurden von hausärztlich tätigen Ärzten und fachärztlich tätigen Internisten unterschiedlich beantwortet: Fachärzte der Inneren Medizin gaben im Mittel 6 bis 7 Tage (4,3; 9,2) kürzere Abstände für die INR-Kontrolle an als ihre hausärztlich tätigen Kollegen (12,9 ± 8,5 Tage vs. 19,7 ± 6,6 Tage; p < 0,0001). Im Vergleich zu den Messungen der medizinischen Regelversorgung schätzten die befragten Internisten die INR-Kontrollabstände um zehn Tage kürzer ein; demgegenüber ergab sich bei hausärztlich tätigen Ärzten eine Differenz zwischen Schätzung und den Daten der medizinischen Regelversorgung von nur zwei Tagen. Die Häufigkeit von Komplikationen infolge der VKA-Therapie wurde von fachärztlich tätigen Internisten 2,1-fach höher eingeschätzt als von hausärztlich tätigen Ärzten (11,1 % pro Jahr [9,4 %; 12,8 %] vs. 5,3 % pro Jahr [4,3 %; 6,3 %]). Im Vergleich mit den Daten der medizinischen Regelversorgung zeigte sich eine niedrigere Schätzung der Komplikationsrate bei fachärztlich tätigen Internisten (11,1 % pro Jahr [9,4 %; 12,8 %] vs. 6,3 % pro Jahr [5,2 %; 7,3]) und eine höhere Schätzung bei hausärztlich tätigen Ärzten (5,3 % [4,3 %; 6,4 %] pro Jahr vs. 7,0 % [6,3 %; 7,6 %] pro Jahr).

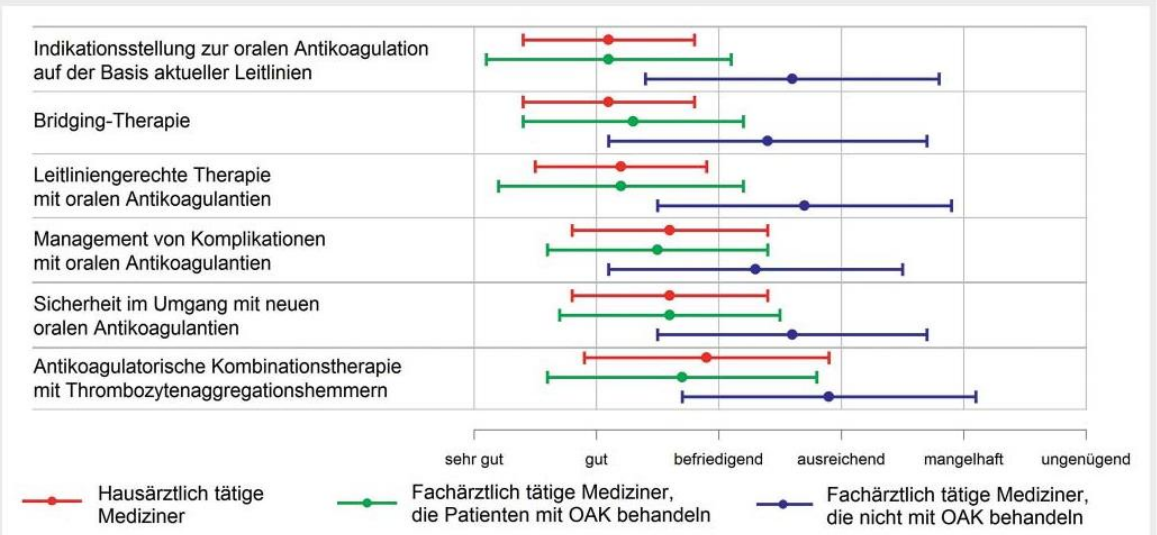
Direkte orale Antikoagulanzien

Von der Mehrheit der befragten OAK-betreuenden Fachärzte (72,4 % [66,0 %; 78,8 %]) bestand eine hohe bis sehr hohe Bereitschaft, DOAK im klinischen Alltag einzusetzen: In der Untergruppe der hausärztlich tätigen Ärzte fiel dieser Anteil geringer aus (36,6 % [25,4 %; 47,8 %]). DOAK wurden bereits vom überwiegenden Anteil der Ärzte, die Patienten mit OAK behandeln, in der Praxis eingesetzt (91,4 % [88,0 %; 94,8 %]). Insgesamt ging die Mehrheit der Befragten nicht davon aus, dass VKA durch die neuen Präparate in den kommenden Jahren vollständig ersetzt werden könnten (hausärztlich tätige Ärzte: 62,0 % [50,7 %; 73,3 %] vs. OAK-betreuende Ärzte: 69,2 % [62,5 %; 73,3 %]). Die meisten Ärzte, die Patienten mit OAK betreuen (88,6 %), setzten DOAK im klinischen Alltag für die folgenden Indikationen ein: Vorhofflimmern (87,9 %), venöse Thromboembolie (73,9 %) und postoperative

▶ **Tab. 2** Einschätzungen zum Fach Hämostaseologie.

	hausärztlich tätige Ärzte (n = 71)	fachärztlich tätige Ärzte, die Patienten mit OAK behandeln (n = 185)	fachärztlich tätige Ärzte, die Patienten nicht mit OAK behandeln (n = 198)
Zunahme der Komplexität des Gebietes Hämostaseologie – (%) (n)	42,2 (30)	56,2 (104)	62,6 (124)
Zustimmung zur Notwendigkeit einer Spezialisierung auf dem Gebiet der Hämostaseologie – (%) (n)	36,6 (26)	67,6 (125)	73,7 (146)
Zustimmung zur Notwendigkeit einer Weiterbildung zum Facharzt für Hämostaseologie – (%) (n)	32,4 (23)	44,9 (83)	47,0 (93)

Die Prozentangaben der einzelnen Gruppen beziehen sich auf den Anteil von Ärzten, der der jeweiligen Aussage zustimmt.



▶ **Abb. 1** Beurteilungen des eigenen Fachwissens zur oralen Antikoagulation. Die Ergebnisse sind auf einer sechsstufigen Skala („sehr gut" bis „ungenügend") ± Standardabweichung in der jeweiligen Kategorie dargestellt.

Thromboseprophylaxe (30,9 %). Eine Übersicht der berichteten Argumente für die Bevorzugung von DOAK im Vergleich zu VKA zeigt ▶ **Abb. 2**. Es handelt sich hierbei um ein Fragenformat mit vordefinierten Antwortmöglichkeiten.

Versorgungsmedizinische Aspekte

Die Mehrheit aller Ärzte (73,8 % [69,7 %; 77,9 %]) stand der Einrichtung einer 24h-Service-Hotline zur medizinischen Beratung im Bereich der klinischen Hämostaseologie positiv gegenüber. Ein spezialisierter Gerinnungsdienst zur Betreuung von Patienten mit OAK wurde ebenfalls mehrheitlich als positiv bewertet (67,3 % [62,9 %; 71,6 %]). Allgemein wären zwei von drei befragten Ärzten bereit, ihre Patienten in Bezug auf das OAK-Therapiemanagement von einem spezialisierten Dienst betreuen zu lassen (68,6 % [64,3 %; 72,9 %]). Hinsichtlich der Notwendigkeit einer spezialisierten Versorgung stellte sich ein unmittelbarer Zusammenhang zwischen Berufserfahrung und Befürwortung dar: Je mehr Berufserfahrung die befragten Ärzte hatten, desto weniger erachteten sie einen spezialisierten Dienst für sinnvoll ($p < 0{,}001$), unabhängig von der jeweiligen Fachrichtung oder Arztbezeichnung. In der Untergruppe der hausärztlich tätigen Ärzte waren die Befürwortung einer spezialisierten Versorgung (40,8 % [29,4 %; 52,3 %]) und die Bereitschaft zur gemeinsamen Betreuung von Patienten mit OAK geringer (46,5 % [34,9 %; 58,1 %]). Unter Ärzten, die eine Therapie mit OAK nicht selbst durchführen, war die Fürsprache einer Einführung eines spezialisierten Gerinnungsdienstes am höchsten (75,3 % [69,1 %; 81,4 %]). Eine Übersicht von Aufgabenbereichen für eine spezialisierte Versorgungseinrichtung zur OAK-Therapie ist in ▶ **Abb. 3** dargestellt. Es handelt sich hierbei um ein Fragenformat mit vordefinierten Antwortmöglichkeiten.

▶ **Tab. 3** Vergleich von ärztlicher Einschätzung und objektiven Versorgungsdaten hinsichtlich der Behandlung mit oralen Antikoagulanzien.

	Qualität der Behandlung mit oralen Antikoagulanzien							
	Selbsteinschätzung in der Befragung				Daten der Regelversorgung[1]			
	hausärztlich tätige Ärzte (n = 73)		Internisten (n = 83)		durch Hausärzte betreut (n = 1093)		durch Internisten betreut (n = 351)	
	Durchschnittswert (95 %KI)	Variabilität (SD)	Durchschnittswert (95 %KI)	Variabilität (SD)	Durchschnittswert (95 %KI)	Variabilität (SD)	Durchschnittswert (95 %KI)	Variabilität (SD)
Zeit im therapeutischen Bereich (%)	77,1 (72,8; 81,3)	18,1	71,6 (69,2; 74,1)	11,1	65,8 (64,1; 67,5)	24,6	69,6 (67,1; 72,0)	21,8
Komplikationsrate[2] (% pro Jahr)	5,3 (4,3; 6,3)	4,4	11,1 (9,4; 12,8)	7,7	7,0 (6,3; 7,6)	n.a.	6,3 (5,2; 7,3)	n.a.
Kontrollabstände (Tage)	19,7 (18,1; 21,2)	6,6	12,9 (11,0; 14,8)	8,5	21,7 (21,0; 22,5)	12,9	22,9 (21,5; 24,3)	13,2

Die Angaben zur Selbsteinschätzung beziehen sich auf Ärzte, die das Management der OAK-Therapie übernehmen. Bei n = 73 (von insgesamt n = 74) hausärztlich tätigen Ärzten und n = 83 Internisten (von insgesamt n = 95) lagen Angaben zur Selbsteinschätzung in der Befragung vor.

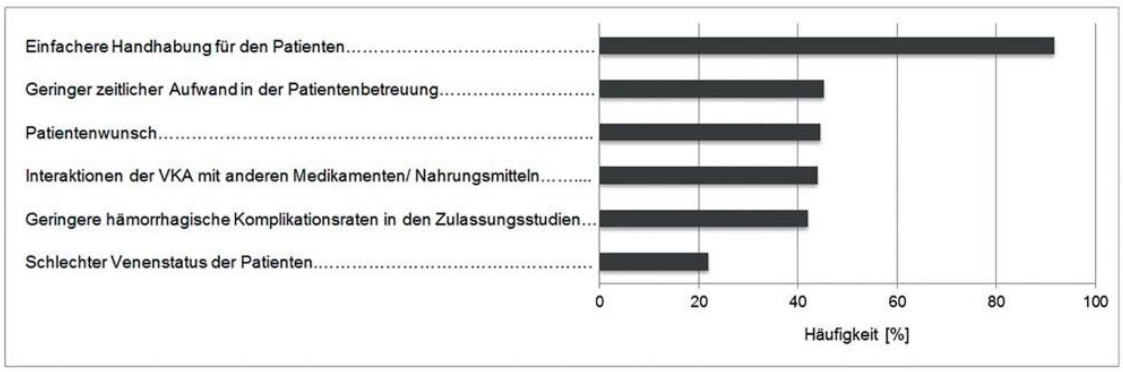
[1] Ergebnisse beruhen auf Auswertungen der Versorgungsdaten der Kohorte der medizinischen Regelversorgung des thrombEVAL-Studienprogramms.

[2] Die Angaben zu Komplikationen in der Kohorte der Regelversorgung umfassten Major-Blutungen und thromboembolische Ereignisse. 95 %KI: 95 % Konfidenzintervall, SD: Standardabweichung, n.a: nicht anwendbar.

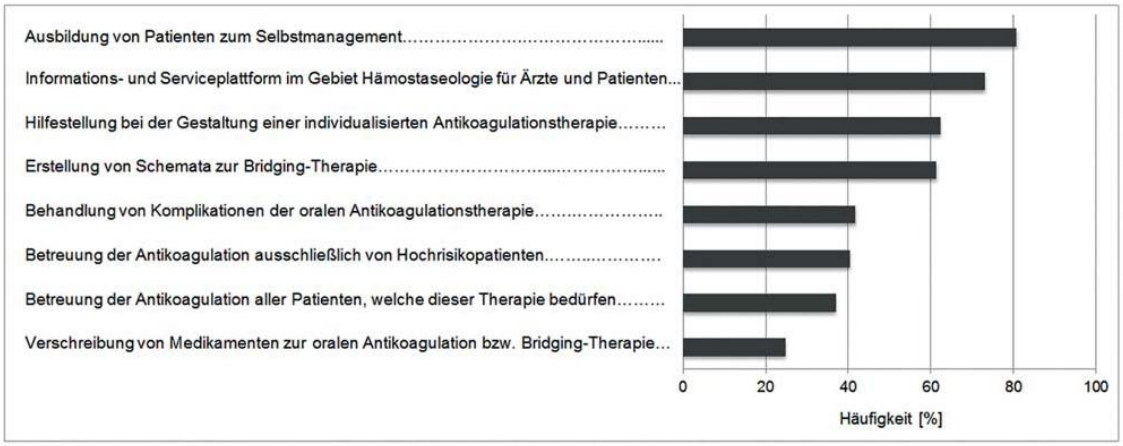
Diskussion

Die vorliegende Untersuchung zeigt, dass Ärzte die aktuelle Versorgungsqualität auf dem Gebiet der OAK-Therapie als „befriedigend" einstufen, aber dennoch ein hohes Optimierungspotenzial in der Versorgung von OAK-Patienten sehen. Hinsichtlich der Einschätzung von Therapiequalität und Komplikationsraten ergaben sich Unterschiede zwischen ärztlicher Einschätzung und aktuellen Versorgungsdaten, aber auch Unterschiede innerhalb der Ärztegruppen. Die am häufigsten vorgeschlagenen Ansatzpunkte zur Verbesserung der Versorgungssituation waren eine intensivere Weiterbildung der Ärzte, die Schulung von Patienten sowie die Bereitstellung von Versorgungsangeboten mit spezialisierter Expertise zum Thema OAK-Therapie. Sowohl eine permanent verfügbare Beratungshotline, als auch ein spezialisierter Gerinnungsdienst werden von der Mehrheit der Ärzte zur Verbesserung der medizinischen Versorgung mit OAK befürwortet.

VKA werden neben der Therapie mit DOAK auch in Zukunft eine immer noch wichtige Rolle in der Antikoagulation spielen, z. B. für Patienten, die DOAK nicht vertragen, aber auch für Indikationsgebiete, die momentan nicht durch DOAK abgedeckt sind (z. B. mechanischer Herzklappenersatz) [10]. In der thrombEVAL-Studie konnte gezeigt werden, dass in Deutschland ein großes Verbesserungspotenzial bezüglich der Therapiequalität mit VKA besteht [7]. Studien in anderen Ländern weisen ebenfalls auf dieses Optimierungspotenzial hin [11]. Dies ist für Patienten mit OAK-Therapie insofern von großer Bedeutung, da ein direkter Zusammenhang zwischen Einstellungsqualität der OAK-Therapie (TTR) und Komplikationsraten besteht [12]. Unklar ist, wie stark die Adhärenz bei Patienten mit DOAK die Komplikationsrate beeinflusst. Besonders gefährdet sind hierbei geriatrische, multimorbide Patienten, die oft einem erhöhten Schlaganfallrisiko aufgrund von verbesserungswürdiger Therapiequalität oder Unterversorgung mit OAK ausgesetzt sind [13]. In der vorliegenden Untersuchung wurde die Therapiequalität von Hausärzten überraschend hoch eingeschätzt. Demgegenüber entspricht die Selbsteinschätzung der Therapiequalität durch die Internisten weitestgehend der Schätzung aus den Daten der medizinischen Regelversorgung. Über die möglichen Ursachen (z. B. möglicherweise unterschiedliches Patientengut oder differierende fachliche Expertise) kann jedoch nur spekuliert werden. Die mit zunehmender Berufserfahrung begleitenden höheren Angaben zur TTR-Einschätzung sind wahrscheinlich auch auf eine höhere Selbstsicherheit in der Behandlung mit OAK und auf eine größere Anzahl durchgeführter Therapien zurückzuführen [14]. Die Literatur zeigt auf, dass hausärztlich tätige Ärzte die Komplikationsrate aufgrund einer Therapie mit oralen Antikoagulanzien höher einschätzen als fachärztlich tätige Internisten [15, 16]. Dieser Sachverhalt steht im Kontrast zu den Ergebnissen dieser Umfrage. Mögliche Erklärungen sind, dass die letztgenannte Arztgruppe einen höheren Anteil an Patienten behandelt, welche aufgrund von Komorbiditäten und komplexer Medikation ein erhöhtes Risiko für Komplikationen aufweisen und folglich engmaschigerer INR-Kontrollen



▶ **Abb. 2** Gründe für die Präferenz direkter oraler Antikoagulanzien im Vergleich zu Vitamin-K-Antagonisten. Die Angaben beruhen auf den Antworten von n = 301 Ärzten im Rahmen der Onlinebefragung. Mehrfachnennungen sind möglich. VKA: Vitamin-K-Antagonisten.



▶ **Abb. 3** Anforderungsprofil an spezialisierte Gerinnungsdienste für die Therapie mit oralen Antikoagulanzien aus Sicht der Ärzte. Die Angaben beruhen auf den Antworten von n = 443 Ärzten im Rahmen der Onlinebefragung. Mehrfachnennungen sind möglich.

bedürfen, aber auch eine höhere Sensibilisierung für OAK-spezifische Komplikationen.

In der Analyse zeigten die befragten Ärzte eine hohe Bereitschaft, DOAK im klinischen Alltag einzusetzen. Dies ist in Übereinstimmung mit den Daten des Arzneimittelreports 2016, in dem ein Anstieg der Verordnungen für DOAK von 3,4 Millionen definierter Tagesdosen in 2011 auf 253,2 Millionen in 2015 zu verzeichnen ist [1]. Da die Verordnungszahlen für VKA nur in einem geringen Maß zurückgehen, ist davon auszugehen, dass sich der Einsatz von DOAK überwiegend auf Patienten mit neu initiierter Antikoagulationstherapie bezieht. DOAK könnten somit dazu beitragen, die Lücke in der Versorgung mit OAK zu schließen, jedoch ist der Einsatz – trotz vorteilhafter Eigenschaften (u. a. einheitliche Dosis ohne Notwendigkeit der Anpassung bzw. Kontrolle) – nicht für alle Indikationen zur OAK-Therapie möglich (z. B. Patienten mit peripherem Bypass bei peripher-arterieller Verschlusskrankheit) [17]. Die Ergebnisse von Phase-IV-Studien zu Komplikationsraten von DOAK im täglichen Einsatz werden aktuell noch kontrovers diskutiert [18 – 20]. Aus versorgungsmedizinischer Sicht ergeben sich zusammenfassend zwei Notwendigkeiten: Zum einen muss die Qualität der Versorgung für Patienten unter VKA weiter optimiert werden, da diese im klinischen Alltag weiterhin in relevanter Zahl eingesetzt werden und die oben beschriebenen Einschränkungen für den Einsatz von DOAK (noch) bestehen. Zum anderen werden dringend weitere wissenschaftlich fundierte Untersuchungen zur Therapie mit DOAK im Hinblick auf die Therapieadhärenz – gerade in der Langzeittherapie –, die sachgerechte Anwendung (z. B. adäquate Dosierung) und das Management von Komplikationen benötigt, auf deren Basis konkrete Handlungsempfehlungen für den medizinischen Alltag

abgeleitet werden können [21]. Dies trifft in besonderem Maße für die Hochrisikogruppe geriatrischer Patienten zu, bei denen trotz vorhandener Therapieindikation (und fehlenden absoluten Kontraindikationen) weiterhin von einer Unterversorgung mit OAK ausgegangen wird und für die die wissenschaftliche Evidenz zu direkten oralen Antikoagulanzien limitiert ist [22]. Die Ergebnisse der vorliegenden Untersuchung geben keinen Anhalt dafür, dass vonseiten der Ärzte grundlegend Bedarf für eine Änderung der ärztlichen Weiterbildung, z. B. durch Einrichtung einer spezifischen Facharztausbildung, auf dem Gebiet der klinischen Hämostaseologie gesehen wird. Im Hinblick auf Optimierungsmöglichkeiten der Versorgung von OAK-Patienten in Deutschland geht aus der Untersuchung hervor, dass die Bereitstellung spezifischer Expertisen wie z. B. eine Beratungshotline oder auch ein spezialisierter Gerinnungsdienst befürwortet wird. Bezüglich telefonischer Beratungsangebote konnten bereits positive Erfahrungen im Bereich der Herzinsuffizienztherapie gemacht werden; hierbei zeigte sich sowohl bei betreuenden Ärzten als auch bei Patienten eine hohe Akzeptanz der standardisierten und spezialisierten Versorgung [23, 24]. Für die Betreuung von OAK-Patienten sind ausführliche Beratung, Dokumentationsqualität, kontinuierliches Monitoring, Patienteninformation sowie Wissen über Nebenwirkungen und Medikamenteninteraktion von großer Bedeutung, um das Auftreten von Komplikationen zu minimieren [25, 26]. In der Literatur finden sich außerdem Hinweise, dass die Kombination aus allgemeinärztlicher Therapie und begleitender spezialisierter Betreuung das klinische Outcome von Patienten deutlich verbessern kann [27]. Studien belegen, dass Patienten, deren OAK-Therapie durch einen spezialisierten Gerinnungsdienst gesteuert ist, eine deutlich höhere Behandlungsqualität mit niedrigerer Komplikationsrate erfahren, was unter anderem in der besonderen Berücksichtigung spezifischer Begleiterkrankungen (z. B. Nieren- und Leberinsuffizienz) und deren Therapie begründet liegen kann [8, 28]. Inwiefern eine spezialisierte Betreuung für Patienten mit DOAK von Vorteil ist, ist aktuell noch Gegenstand wissenschaftlicher Untersuchungen [29].

Limitationen

Aufgrund der Teilnahmerate, die bei ärztlichen Umfragen erwartungsgemäß niedrig ist [30], kann eine Verzerrung der Ergebnisse durch Über- bzw. Unterrepräsentation einzelner Gruppen im Sinne eines „response bias“ nicht ausgeschlossen werden. Es ist denkbar, dass die Mehrheit der befragten Ärzte sich aufgrund des spezifischen Themengebietes nicht angesprochen fühlte und/oder dass vor allem Ärzte an der Befragung teilgenommen haben, die das Thema besonders interessierte, oder die diesbezüglich Bedenken hatten. Interpretationen hinsichtlich der Gesamtpopulation sollten basierend auf den Daten der vorliegenden Studie aufgrund der geringen Teilnahmerate mit Vorsicht vorgenommen werden. Wie von wissenschaftlichen Analysen belegt wurde, bedeutet eine niedrige Rücklaufquote jedoch nicht zwangsläufig, dass Schätzungen einer Umfrage ungenau oder nicht-repräsentativ sind [31, 32]. Eine Nonresponder-Analyse, um die Gründe für die Ablehnung der Teilnahme zu erörtern, wurde nicht durchgeführt. Es gilt zu bedenken, dass die subjektive Einschätzung der TTR wie auch deren Berechnung und die Erfassung von Komplikationsraten methodischen Limitationen unterliegen. Informationen zu möglichen Gründen für die Präferenz von Vitamin-K-Antagonisten im Vergleich zu DOAK wurden im Rahmen der Onlinebefragung nicht erfasst. Aufgrund der Durchführung der thrombEVAL-Studie in Rheinland-Pfalz ist die Übertragung der Ergebnisse auf die Bundesebene bzw. die gesamte Ärzteschaft nicht uneingeschränkt zulässig.

KERNAUSSAGEN

- Die Versorgungsqualität im Bereich der Therapie mit oraler Antikoagulation wurde von den befragten Ärzten im Durchschnitt als „befriedigend“ eingestuft.
- Es besteht ein hoher Bedarf an Beratung und Schulung auf dem Gebiet der oralen Antikoagulationstherapie aus Sicht der Ärzte.
- Die Mehrheit der befragten Ärzte bewertete die Einrichtung spezialisierter Angebote (z. B. Beratungshotline oder Gerinnungsdienst) für das Management der Therapie mit oralen Antikoagulanzien positiv.

Interessenkonflikt

Prof. Dr. Wild erklärt, dass er für die Durchführung des thrombEVAL-Studienprogramms (Studiensponsor ist die Universitätsmedizin Mainz), zu dem auch die vorliegende Untersuchung gehört, Forschungsunterstützung von der Initiative Gesundheitswirtschaft Rheinland-Pfalz (Gesundheitsministerium und Wirtschaftsministerium Rheinland-Pfalz, AZ.623 – 1), dem Bundesministerium für Bildung und Forschung (BMBF 10E01003), Boehringer Ingelheim Pharma GmbH & Co. KG, Bayer Vital GmbH, Daiichi Sankyo Europe GmbH, Sanofi-Aventis Germany GmbH, IMO Institut GmbH, Portavita B.V. und der Deutschen Herzstiftung erhalten hat. Die übrigen Autoren berichten keine Interessenskonflikte. Die Sponsoren hatten keinen Einfluss auf das Studiendesign, die Durchführung der Studie, die Analyse und Interpretation von Daten oder die Entscheidung zur Publikation.

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Relevance of polypharmacy for clinical outcome in patients receiving vitamin K antagonists

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Relevance of Polypharmacy for Clinical Outcome in Patients Receiving Vitamin K Antagonists

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BACKGROUND: Although polypharmacy is associated with a negative clinical outcome in various settings and commonly observed in patients receiving oral anticoagulation therapy, evidence on the relevance for the clinical outcome of anticoagulated patients is currently limited. The aim of the study was to investigate the effect of polypharmacy on the clinical outcomes among patients taking phenprocoumon.

DESIGN: Prospective cohort study.

SETTING: Regular medical care.

PARTICIPANTS: Information on 2011 individuals receiving vitamin K antagonists was available for analysis from the prospective multicenter thrombEVAL study.

MEASUREMENTS: Data were obtained from clinical visits, computer-assisted interviews, and laboratory measurements. Information on clinical outcome was obtained during a 3-year follow-up period and subsequently validated via medical records.

RESULTS: The prevalence of polypharmacy (five drugs or more) was 84.1% (n = 1691). Quality of anticoagulation therapy assessed by time in therapeutic range was lower in individuals on five to eight drugs and nine drugs or more (70.7% and 64.7%, respectively) compared with subjects without polypharmacy (73.4%). In addition, a significantly higher variability of international normalized ratio measurements was found in the presence of polypharmacy. The cumulative incidence of bleeding, hospitalization, and all-cause mortality, but not for thromboembolic events, increased across groups of medication. In adjusted Cox regression analysis, polypharmacy is an independent risk factor for bleeding (hazard ratio $[HR]_{\geq 9 \text{ drugs vs } 1\text{-}4 \text{ drugs}} = 1.62$; 95% confidence interval [CI] = 1.04-2.52; $p = .033$); hospitalization ($HR_{\geq 9 \text{ drugs vs } 1\text{-}4 \text{ drugs}} = 1.60$; 95% CI = 1.26-2.03; $p < .001$; and all-cause mortality ($HR_{\geq 9 \text{ drugs vs } 1\text{-}4 \text{ drugs}} = 2.16$; 95% CI = 1.43-3.27; $p < .001$) in a dose-dependent relationship. Per additional drug, bleeding risk was increased by 4%.

CONCLUSIONS: Polypharmacy influences the quality of anticoagulation therapy and translates into an elevated risk of adverse events in anticoagulated patients. This suggests that additional medication intake in such patients should be critically reviewed by physicians, and it highlights the importance of initiating investigations aimed at reducing multiple medication intake. **J Am Geriatr Soc 67:463–470, 2019.**

Key words: anticoagulant drugs; hemorrhage; multimorbidity; phenprocoumon; polypharmacy

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Demographic changes with increasing life expectancy will lead to a growing number of patients with multiple chronic conditions in the near future.[1] Multimorbidity is commonly accompanied by the use of multiple drugs in a single patient, a condition known as polypharmacy,[2] most often defined as a constant intake of more than four drugs by a patient. It is increasingly prevalent in daily clinical

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practice.[3–5] Unfortunately, polypharmacy was described as associated with a higher risk of adverse drug reactions, drug-drug interactions, poor adherence to medical therapy, lower quality of life, and a higher frequency of hospitalization.[6,7]

Vitamin K antagonists (VKAs) are known to interact with various prescription and over-the-counter medicines and increase the risk of bleeding, which makes it important to closely monitor VKA-treated patients on multiple medications.[8] In this context, anticoagulated subjects with polypharmacy often have an unpredictable dose-response relationship to oral anticoagulation, in which polypharmacy was shown to be a risk indicator for cardiac death and anticoagulation-related events such as bleeding and thromboembolic events.[9,10] In the context of direct-acting oral anticoagulants (DOACs), data from the ROCKET-AF, ARISTOTLE, and Hokusai-VTE trials suggested that DOACs are more effective than and at least as safe as warfarin, regardless of the number of drugs taken.[10–12] However, due to different pharmacokinetic properties of phenprocoumon and warfarin, the clinical outcome of patients receiving long-acting VKA phenprocoumon might vary from recent reports with warfarin. There have not yet been any studies investigating the association between polypharmacy, quality of oral anticoagulation therapy, and clinical outcome in subjects taking phenprocoumon.

Therefore, the aim of this analysis was to evaluate the impact of polypharmacy on the quality of anticoagulation therapy and subsequent clinical outcome in patients receiving the long-acting VKA phenprocoumon.

METHODS

Study Design

The rationale and design of the thrombEVAL study (ClinicalTrials.gov identifier NCT01809015) were previously described.[13] Briefly, the thrombEVAL study program comprises two prospective observational studies that investigated the quality of oral anticoagulation therapy in regular medical care and in a telemedicine-based coagulation service, both located in Rhineland-Palatinate, midwestern Germany. The study protocol conforms to the ethical guidelines of the Declaration of Helsinki as reflected in the a priori approvals by the local responsible Ethics Committee and the local data safety commissioner. All participants provided informed written consent to participate in this study.

Study Sample and Data Assessment

Between January 2011 and April 2, 2013, 2011 subjects were enrolled in the regular care cohort. The baseline examination comprised a standardized assessment of clinical status, sociodemographic variables, anthropometric measurements, medication, need for nursing care, and laboratory examinations. All study information underwent detailed quality control for completeness, plausibility, and validity according to prespecified criteria. Measurements of international normalized ratio (INR) values were collected retrospectively from study entry and during follow-up using inpatient laboratory data and the patients' anticoagulant card in regular medical care. The time in therapeutic range (TTR) was calculated according to the Rosendaal method.[14] Risk of stroke and major bleeding was determined according to the CHA_2DS_2-Vasc and HAS-BLED score, respectively.[15,16] Due to the nature of the study, design follow-up information was available for 1558 subjects.

Assessment of Polypharmacy

Medication use was defined as regular use (daily or weekly) and individually recorded from the prescription plan including active substances and daily doses of the medication. Drugs were coded according to the World Health Organization's Anatomical Therapeutic and Chemical (ATC) classification system.[17] The corresponding ATC codes are summarized in Supplementary Table 1. The analysis was based on the number of active substances and referred to as "number of drugs/medication" in this article. Drugs known to inhibit or potentiate the anticoagulant effect were studied and categorized according to the latest version of the summary of product characteristics form of phenprocoumon and warfarin.[18,19] Subjects were divided into the following three groups according to the number of concomitant medications (all participants taking at least one VKA): one to four, five to eight, or nine or more different medications.

Outcome Assessment

The clinical outcome comprised both anticoagulation-specific and non-anticoagulation-specific events: clinically relevant bleeding as a composite of major bleeding and clinically relevant nonmajor bleeding, and thromboembolic events defined as the occurrence of thrombosis, pulmonary embolism, systemic embolism, stroke, or myocardial infarction. Non-anticoagulation-specific events were defined as hospitalization and all-cause mortality.

Information on study end points was assessed in electronic case report forms via annual computer-assisted interviews with the study participants or from medical records. For all information on study end points, source data were obtained to evaluate validity. Subsequent adjudication of all reported end points was carried out by independent reviewers. In addition, electronic database systems of hospital records were screened for unreported events to reduce a potential recall bias. All-cause mortality was assessed via regular checks of the vital status at the registration offices.

Statistical Analysis

Baseline characteristics of the sample were expressed as absolute numbers and percentages for categorical variables, and medians with 25th and 75th percentile and means with corresponding standard deviation for continuous data. Disease burden was assessed using the age-adjusted Charlson Comorbidity Index (CCI).[20] Cumulative incidences were plotted graphically indicating the number of participants at risk in intervals of 4 months and for each outcome. Rate ratios (RRs; events per 100 patient-years) with corresponding 95% confidence interval (CIs) were calculated for outcome events according to categories of drug intake. Cox regression models with hazard ratios (HRs) with 95% CIs adjusted for potential confounders such as age, sex, traditional cardiovascular risk factors, and comorbidities were calculated to evaluate the effect of polypharmacy on the

outcome. High-risk subgroups for bleeding per se were defined a priori and screened for potential interactions. All statistical analyses were conducted using the software program R, v.3.1.1 (http://www.r-project.org).

RESULTS

Baseline Characteristics and Comorbidities of Study Sample

Table 1 includes details of the demographic and clinical characteristics of the study population, categorized by the individual's number of drugs. The prevalence of polypharmacy in the study sample was 84.1%, with a prevalence of 44.7% for moderate polypharmacy (intake of five to eight drugs) and 39.4% for marked polypharmacy (intake of nine or more drugs), respectively. The median age of the study sample was 73.0 years (interquartile range [IQR] = 66.0-79.0), and 62.2% were male. The prevalence of most comorbidities and traditional cardiovascular risk factors increased significantly with the number of drugs. This trend was also reflected by the CCI. Also, the scores of risk measures such as CHA_2DS_2-Vasc and HAS-BLED increased with polypharmacy.

Concomitant Medication Use

The mean number of medications used in addition to oral anticoagulation at baseline was 7.76 ± 3.28, with a range from zero to 24 (Supplementary Figure 1). Overall, 98.3% of study participants received phenprocoumon as an oral anticoagulant. The most commonly taken co-medications in the whole study population were diuretics and β-blocking agents (Supplementary Table 2). The frequency of concomitant medications known to increase or decrease the INR values (as listed in the recent summary of product characteristics for phenprocoumon and warfarin) and used by more than 5% of the study sample are presented in Table 1. The total number of co-medications was also related to increasing use of drugs that potentially influence the INR level stating that anticoagulated subjects with five drugs or more were using those drugs six times more frequently than participants on one to four drugs only. The most frequently used drugs that potentially influence the INR level in the group of subjects with five drugs or more were diuretics (72.9%), statins (46.6%), and low-dose acetylsalicylic acid (19.9%); in the medication classes not known to interact with VKA, it was β-blocking agents (67.4%), angiotensin-converting enzyme inhibitors (43.6%), and proton pump inhibitors (37.1%).

Polypharmacy and Quality of Anticoagulation Control

Figure 1 outlines the quality of anticoagulation treatment stratified by the number of concomitant medications. Participants on nine or more drugs spend a significantly lower proportion of TTR compared with individuals on five to eight and one to four drugs, pattern A. In addition, the relative difference in time below the target range between medication groups is smaller than the relative difference in time above the target range (63% vs 88%), indicating a bigger shift toward higher INR values, pattern B.

Table 1. Baseline Characteristics of Study Participants (N = 2011) by Medication Intake

	Polypharmacy		
	No (1-4 drugs)	Moderate (5-8 drugs)	Marked (≥9 drugs)
	N = 320	N = 899	N = 792
Age, y (interquartile range)	68.0 (54.0-76.0)	73.0 (66.0-79.0)	75.0 (69.0-81.0)
Male sex, % (n)	67.8 (217)	59.0 (530)	63.6 (504)
Risk measures, mean (SD)			
Charlson Comorbidity Index	4.32 (2.46)	5.69 (2.21)	6.69 (2.04)
CHA_2DS_2-Vasc[a]	2.98 (1.81)	3.95 (1.66)	4.78 (1.56)
HAS-BLED[a]	2.11 (1.27)	2.70 (1.14)	3.47 (1.21)
Comorbid diseases, % (n)			
Atrial fibrillation	55.8 (178)	74.7 (668)	77.3 (606)
Chronic kidney disease	12.6 (40)	17.2 (154)	32.1 (253)
Congestive heart failure	20.6 (65)	38.5 (339)	52.6 (409)
Coronary artery disease	18.6 (58)	34.0 (294)	55.2 (421)
Current smoking	9.7 (31)	7.1 (64)	5.1 (40)
Diabetes	9.7 (31)	25.8 (231)	44.9 (355)
Dyslipidemia	34.7 (111)	50.4 (452)	60.6 (480)
History of bleeding	28.8 (89)	27.2 (235)	32.8 (247)
Hypertension	54.1 (173)	80.9 (727)	87.2 (690)
Liver disease	4.7 (15)	4.9 (44)	6.8 (53)
Obesity	25.0 (80)	27.5 (247)	36.5 (289)
Peripheral artery disease	16.0 (51)	20.2 (177)	23.3 (180)
Prior deep vein thrombosis	30.9 (99)	15.2 (135)	15.9 (125)
Prior pulmonary embolism	18.1 (58)	8.6 (77)	10.9 (86)
Prior stroke/TIA	13.8 (44)	15.8 (142)	20.6 (162)
Positive family history of cardiovascular disease	36.6 (117)	37.2 (334)	40.1 (317)
Co-medication potentially interacting with VKA, % (n)			
Increases INR and risk of bleeding			
Allopurinol	1.2 (4)	12.6 (113)	26.9 (213)
Antiarrhythmic agents	6.2 (20)	12.3 (111)	14.0 (111)
Antidepressants	1.2 (4)	6.8 (61)	15.7 (124)
NSAIDs	0.6 (2)	4.4 (40)	8.5 (67)
Opioids	0.9 (3)	3.4 (31)	14.8 (117)
Platelet aggregation inhibitors	5.9 (19)	14.0 (126)	32.6 (258)
Statins	4.7 (15)	35.9 (323)	58.7 (465)
Decreases INR and increases risk of thromboembolic events			
Corticosteroids	0.3 (1)	3.1 (28)	10.6 (84)
Digitalis	3.8 (12)	10.9 (98)	18.9 (150)
Diuretics	9.4 (30)	59.4 (534)	88.1 (698)
Oral antidiabetic agents	2.8 (9)	12.3 (111)	24.4 (193)
Thyroid hormone treatment	5.0 (16)	14.6 (131)	21.2. (168)

Abbreviations: INR, international normalized ratio; NSAID, nonsteroidal anti-inflammatory drugs; SD, standard deviation; TIA, transient ischemic attack; VKA, vitamin K antagonist.

[a]Score was calculated for all study participants (independent of the presence of atrial fibrillation).

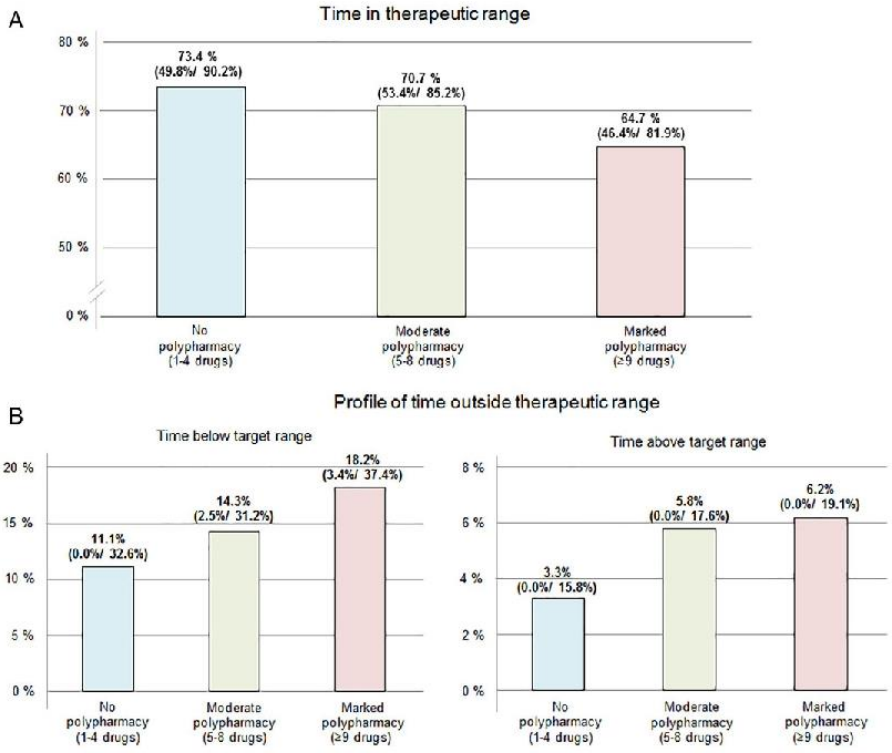

Figure 1. Quality of anticoagulation therapy stratified by the presence of polypharmacy.
The time in therapeutic range was calculated according to the Rosendaal method.[14] Median values with corresponding interquartile ranges are displayed; hence percentages of totals do not add up to 100%.

Clinical Outcome According to the Number of Concomitant Drugs

During a mean follow-up period of 2.3 ± 1.0 years (maximum of 3 y), the overall incidence rates of thromboembolism, bleeding, hospitalization, and all-cause mortality were 3.4, 9.5, 62.8, and 9.6 events per 100 patients-years, respectively. The occurrence of thromboembolic events was not relevantly different with the extent of polypharmacy ($RR_{5\text{-}8\ drugs\ vs\ 1\text{-}4\ drugs}$ = 0.92; 95% CI = 0.53-1.66; p = .86; and $RR_{\geq 9\ drugs\ vs\ 1\text{-}4\ drugs}$ = 1.27; 95% CI = 0.74-2.26; p = .45). However, individuals on nine or more drugs had a higher incidence of clinically relevant bleeding events than subjects on one to four drugs (12.8 events per 100 patient-years vs 5.0 events per 100 patient-years; $RR_{\geq 9\ drugs\ vs\ 1\text{-}4\ drugs}$ = 2.58; 95% CI = 1.74-3.94; $p < .001$), and even subjects on five to eight drugs (12.8 events per 100 patient-years vs 8.5 events per 100 patient-years; $RR_{\geq 9\ drugs\ vs\ 5\text{-}8\ drugs}$ = 1.50; 95% CI = 1.20-1.89; $p < .001$; Supplementary Table 3). The 3-year cumulative incidence of bleeding increased across groups of medications (12.8% for 1-4 drugs; 19.7% for 5-8 drugs; 24.1% for ≥9 drugs). Similar relationships were observed for hospitalizations and all-cause mortality but not for thromboembolic events and the subtype major bleeding (Figure 2 and Supplementary Figure 2).

To evaluate specific effects of concomitant drugs on clinical outcome independent of the clinical profile, adjusted HRs were determined for thromboembolism, clinically relevant bleeding, hospitalizations, and all-cause mortality according to the categories of polypharmacy (Table 2). Marked polypharmacy was found to be independently associated with an increased risk of clinically relevant bleeding, even after adjusting for individuals' cardiovascular risk factors and comorbidities (HR = 1.62; 95% CI, 1.04-2.52; p = .033). Similarly, after adjustment for covariates, participants receiving nine or more drugs had a higher all-cause mortality compared with those taking between one to four drugs (HR = 2.16; 95% CI = 1.43-3.27; $p < .001$). The effects were smaller for the comparison of five to eight drugs vs one to four drugs than for nine or more drugs vs one to four drugs for the outcomes clinically relevant bleeding, hospitalization, and all-cause mortality, thus supporting a kind of dose-response relationship. However, effects were again not observed for the health outcome thromboembolic events (HR = 1.13; 95% CI = 0.60-2.13; p = .72) and the subtype major bleeding (HR = 1.28; 95% CI = 0.74-2.22; p = .37; Supplementary Table 4). When analyzing the number of drugs as the continuous variable, the risk of clinically relevant bleeding was increased by 4% (p = .05) per additional drug. Supplementary analyses regarding the effect of a combination of possible potentiating and/or inhibiting medication did not reveal any relevant associations in relation to thromboembolic events and clinically relevant bleeding (Supplementary Table 5). In Figure 3, sensitivity analyses are displayed for the outcome clinically relevant bleeding for predefined subgroups that reveal a high risk of bleeding

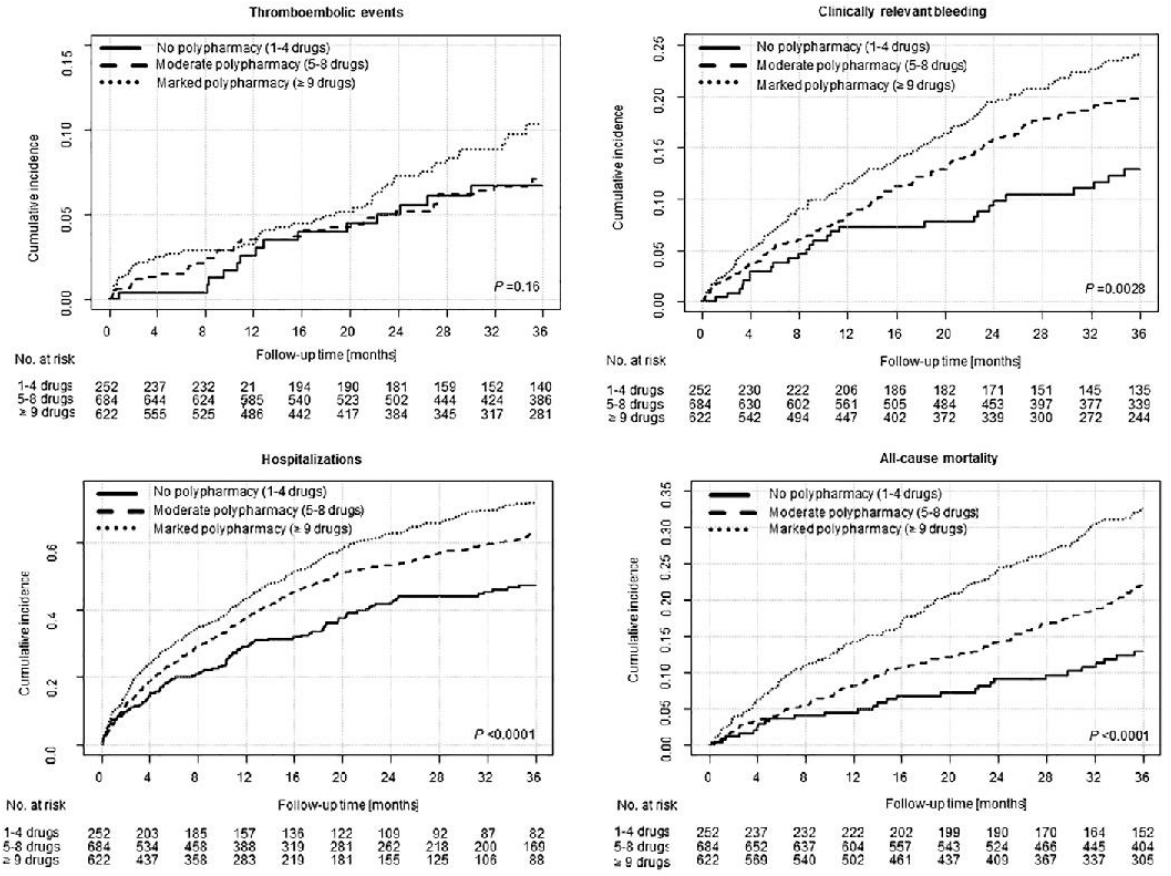

Figure 2. Clinical outcome stratified by the presence of polypharmacy.

per se. No significant interactions, however, were detected between the groups.

DISCUSSION

This study aimed at assessing the consequences of polypharmacy for anticoagulation-specific and nonspecific outcome among participants with oral anticoagulation treatment. To our knowledge, this is the first study investigating the impact of polypharmacy on the quality of anticoagulation therapy and subsequent clinical outcome of patients receiving the long-acting VKA phenprocoumon. In this prospective study of a real-life sample of individuals on oral anticoagulants, 84% of participants were taking five or

Table 2. Effect of Polypharmacy on Clinical Outcome

	Thromboembolic events		Clinically relevant bleeding events		Hospitalizations		All-cause mortality	
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Polypharmacy, categorical variable								
5-8 drugs vs 1-4 drugs (Ref.)	0.92 (0.49-1.71)	.79	1.39 (0.91-2.14)	.13	1.36 (1.08-1.70)	**.079**	1.48 (0.98-2.24)	.062
≥9 drugs vs 1-4 drugs (Ref.)	1.13 (0.60-2.13)	.72	1.62 (1.04-2.52)	**.033**	1.60 (1.26-2.03)	**<.001**	2.16 (1.43-3.27)	**<.001**
Risk per drug, continuous variable	1.00 (0.94-1.07)	.97	1.04 (1.00-1.09)	**.05**	1.04 (1.02-1.07)	**<.001**	1.08 (1.04-1.12)	**<.001**

Abbreviations: CI, confidence interval; HR, hazard ratio.

Note: The Cox regression model was adjusted for age, sex, obesity, diabetes, current smoking, hypertension, dyslipidemia, family history of myocardial infarction or stroke, and the Charlson Comorbidity Index. The *P*-values ≤.05 are shown in boldface type.

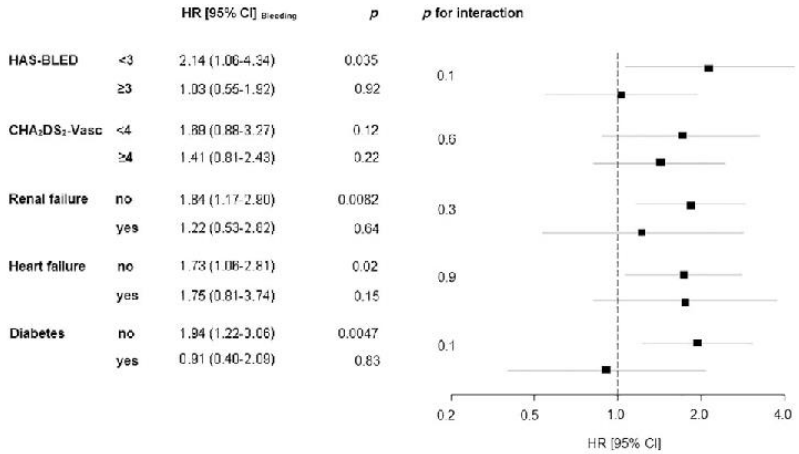

Figure 3. Risk for clinically relevant bleeding in defined high-risk subgroups. CI, confidence interval; HR, hazard ratio.

more medications including their oral anticoagulant. The quality of oral anticoagulation therapy, assessed by TTR and variability of INR measurements, declined with a higher number of drugs. Polypharmacy was related to higher rates of adverse clinical outcomes. Finally, the data demonstrate that polypharmacy was associated with clinically relevant bleeding, hospitalization, and all-cause mortality independent of age, sex, and clinical profile, but not with thrombotic or thromboembolic events.

In general, it is difficult to compare present results with findings of previous studies due to varying classifications of polypharmacy applied in the literature.[21–23] Thus far, there is no consensus definition for polypharmacy, despite an increasing frequency of this condition in clinical practice.[23–25] Previous evidence on the occurrence of polypharmacy among anticoagulated subjects is rare.[26] The prevalence of polypharmacy in the current sample is far higher than rates reported for population-based cohorts (ranging from 4% to 42%).[24,27,28] Despite the challenges faced in comparing polypharmacy investigations, it is clear that polypharmacy is highly prevalent in anticoagulated subjects. This highlights that particular attention should be paid to anticoagulated subjects with polypharmacy who in turn could potentially benefit from more intensive and adequate anticoagulation monitoring.

Prior studies investigated the effect of polypharmacy on a range of health outcomes including falls, adverse drug events, hospitalization, and measures of cognition.[6,29,30] Fewer studies, however, have specifically examined the influence on safety and efficacy end points in oral anticoagulation therapy. In the present analysis on individuals with predominantly phenprocoumon treatment, a high number of drug substances was independently associated with bleeding events, hospitalization, and all-cause mortality. This main finding is in line with previous observations on other anticoagulants.[9–11,31] Focks et al performed a post hoc analysis in the ARISTOTLE trial and argued that polypharmacy is associated with a higher risk of major bleeding (HR = 1.72 for ≥9 vs 0-5 medications; 95% CI = 1.41-2.01; $p < .0001$).[10]

Atrial fibrillation patients are more commonly affected by traditional cardiovascular risk factors and concomitant diseases than participants with other indications for oral anticoagulation therapy (ie, prosthetic heart valves) and hence exhibit a different pattern of drug use.[11,21] Interestingly, patients using four or more medications and who were managed by professional anticoagulation clinics did not experience an elevated risk of major bleeding.[21] Additionally, in the current analysis the number of comedications was not statistically related significantly to the incidence and risk of thromboembolic events. This finding is likely due to limitations of sample sizes to detect differences in infrequent outcomes (eg, thromboembolism). Of note, the occurrence of venous embolism (ie, pulmonary embolism and deep vein thrombosis) was higher among subjects on low drug use. Similar to the present data, various reports have demonstrated that polypharmacy is not associated with systemic embolism or stroke,[9,11] leaving the exact pathologic mechanism to be revealed.[32]

The association between polypharmacy and mortality was also shown by several prior studies[2,9,11,33] but not all.[22,34,35] Importantly, in the present data HRs were higher when comparing the category of one to four drugs to nine or more drugs than to five to eight drugs, which supports a dose-response relationship between polypharmacy and adverse health outcomes.

TTR is known to be a major determinant of efficacy and safety of VKA treatment[36] and is stated to be much lower in the class of nine or more medications compared with the group without polypharmacy in the present analysis. On one hand, this could, at least in part, explain the higher bleeding risk. On the other hand, it should be noted that subjects with high drug use spend a higher proportion both in above but also below the therapeutic target range than patients with low drug use. Thus higher variability of INR measurements in the presence of polypharmacy, which is likely to be caused by drug-drug interactions, might be indicative for the increased bleeding risk. Other reasons for more variable INR measures in the polypharmacy group could be more frequent medication changes, poor adherence, or malignancy.

It cannot be disregarded that a higher drug intake is accompanied by more adverse clinical conditions,[31,37] which

makes the assumption plausible that a larger number of co-medications is simply an indicator of higher comorbidity and mortality.[2,38] Because subjects on severe polypharmacy were older and sicker, the observed association between marked polypharmacy, hemorrhagic events, and all-cause mortality could theoretically at least partly be explained by potential uncontrolled confounders, such as unknown present diseases, acute infections, changes in VKA dosing, or genetic factors. However, in the current analysis, this association was still observed after adjustment for the CCI that covers 19 major disease categories weighted according to their prognostic impact on patient survival.[20]

STRENGTHS AND LIMITATIONS

A key strength of the present study is that, unlike most reports in the literature, it is a real-world study that includes individuals on long-acting VKA phenprocoumon independently of their indication, which leads to a greater generalizability of the results for this patient group. Furthermore, outcome events were adjudicated by a clinical events committee, guaranteeing a high quality of outcome assessment. Finally, to ascertain the association between active substances with adverse health outcome, the analysis was based on the number of active substances rather than the number of drugs.

The study has potential limitations: (1) Data are shown for baseline medication use only. However, subjects with polypharmacy and several chronic medical conditions do not tend to change the number of medications substantially.[39] (2) Unmeasured confounding variables (eg, alcohol abuse, genetic factors, or dietary vitamin K intake) might have influenced the associations. Nevertheless, adjustment for a broad range of clinical conditions was conducted. (3) No information was available on the adherence to pharmacologic drug treatment. Then again, unlike in prescription databases, the self-reported data source (ie, prescription drug plan) is more likely to reflect the actual drug intake by patients. (4) The data set does not include over-the-counter products (eg, ibuprofen, acetylsalicylic acid), herbal remedies (eg, ginseng, *Ginkgo biloba* extract, garlic tablets, ginger), vitamins or dietary supplements (eg, fish oil tablets, cod liver oil), potentially leading to an underestimation of the results.

In conclusion, anticoagulated patients with polypharmacy show a significantly increased risk of bleeding, hospitalizations, and all-cause mortality. These results suggest that additional medication intake in such patients should be critically reviewed by physicians, and they highlight the importance of initiating investigations aimed at reducing multiple medication intake. Due to steadily increasing prescription rates of DOACs and the high prevalence of polypharmacy, future studies are needed to provide scientific evidence on the causal relationship between polypharmacy and hemorrhagic complications, and to understand the molecular mechanisms and potential mediators involved in this relationship.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

Supplementary Table S1. Corresponding Anatomical Therapeutic and Chemical codes for drug groups of interest
Supplementary Table S2. Prevalence of the 10 most common drug groups stratified by polypharmacy status
Supplementary Table S3. Frequency of adverse events by medication intake
Supplementary Table S4. Associations between number of drugs and major bleeding
Supplementary Table S5. Associations between comedication influencing vitamin K antagonist metabolism and clinical outcome
Supplementary Figure S1. Distribution of number of medication in addition to vitamin K antagonist at baseline among 2011 participants
Supplementary Figure S2. Cumulative incidence of major bleeding stratified by number of drugs

SUPPLEMENTAL MATERIAL

Relevance of polypharmacy for clinical outcome in patients receiving vitamin K-antagonists

Running title: Polypharmacy and clinical outcome

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Table of Contents

Supplemental Table 1: Corresponding ATC Codes for drug groups of interest

Drug group	ATC-Codes
ACE inhibitors	C09
Acetylsalicylic acid (low dose)	B01AC06; B01AC34; B01AC36; B01AC56
Allopurinol	M04AA01
Angiotensin II receptor antagonists	C09C; C09D
Antiarrhythmic agents	C01B
Antibiotics	J01
Antidepressants	N06A
Antithyroid agents	H03
Benzodiazepines	N05CA; N03AE; N05B; N05CD
Beta blocking agents	C07
Bisphosphonates	M05BA; M05BB
Calcium channel blockers	C08; C09BB; C09DB
Clopidogrel	B01AC04
Corticosteroids	H02A; H02B
Digitalis	C01AA
Diuretics	C03
Drugs for obstructive airway diseases	R03
Insulin	A10A
NSAIDs	A01AD05; N02BA01; N02BA51; N02BA71; R05XA02; M01BA03; C10BX01; C10BX01; C10BX02; C10BX04; C10BX05; N02AA66; M01AE14; C01EB16; G02CC01; M01AE01; M02AA13; R02AX02; M01AE51; M01AE09; M02AA19; R02AX01; S01BC04; G02CC02; 01AE02; M02AA12; M01AE52; M01AE56; M01AE17; M02AA27; M01AE03; M02AA10; M01AE53; M01AE11; D11AX18; M01AB05; M02AA15; S01BC03; S01CC01; M01AB55; C01EB03; M01AB01; M02AA23; S01BC01; S01CC02; M01AB51; M01AC01; M02AA07; S01BC06; M01AC02; M01AC06; M01AC56; M01AH04; M01AH05; L01XX33; M01AH01
Opioids	N02A
Oral antidiabetic agents	A10B
Proton pump inhibitors	A02BC; B01AC56
Statins	B01AC56; C10AA

Supplemental Table 2: Prevalence of the most ten most common drug groups stratified by polypharmacy status

	Polypharmacy		
	No (1-4 drugs) N=320	**Moderate (5-8 drugs)** N=899	**Marked (≥ 9 drugs)** N=792
Diuretics	9.4 (30)	59.4 (534)	88.1 (698)
Beta blocking agents	27.5 (88)	63.0 (566)	72.5 (574)
Statins	4.7 (15)	35.9 (323)	58.7 (465)
ACE-Inhibitors	10.6 (34)	38.2 (343)	49.9 (395)
Proton pump inhibitors	5.9 (19)	23.0 (207)	53.2 (421)
Angiotensin II receptor antagonists	5.6 (18)	26.1 (235)	32.6 (258)
Calcium channel blockers	4.1 (13)	19.8 (178)	32.8 (260)
Acetylsalicylic acid (low dose)	5.0 (16)	12.2 (110)	28.7 (227)
Allopurinol	1.2 (4)	12.6 (113)	26.9 (213)
Thyroid hormone treatment	5.0 (16)	14.6 (131)	21.2 (168)

Supplemental Table 3. Frequency of adverse events by medication intake

	1-4 drugs (N=320)		5-8 drugs (N=899)		≥ 9 drugs (N=792)	
	Events No.	**Event rate: No./ 100 py**	**Events No.**	**Event rate: No./ 100 py**	**Events No.**	**Event rate: No./ 100 py**
Thromboembolic events	19	3.14	48	2.90	54	3.98
Clinically relevant bleeding	30	4.96	141	8.53	174	12.81
- major bleeding	20	3.31	90	5.44	90	6.63
Hospitalization	245	40.52	986	59.64	1039	76.48
All-cause mortality	28	4.63	136	8.23	184	13.54

No., number; py, patient-years

Supplemental Table 4: Associations between number of drugs and major bleeding

	Major bleeding		
	HR	**95% CI**	**p**
Polypharmacy as categorical variable			
5-8 drugs vs. 1-4 drugs	1.30	0.77-2.18	0.33
≥ 9 drugs vs. 1-4 drugs	1.28	0.74-2.22	0.37
Risk per drug (continuous variable)	1.01	0.95-1.06	0.80

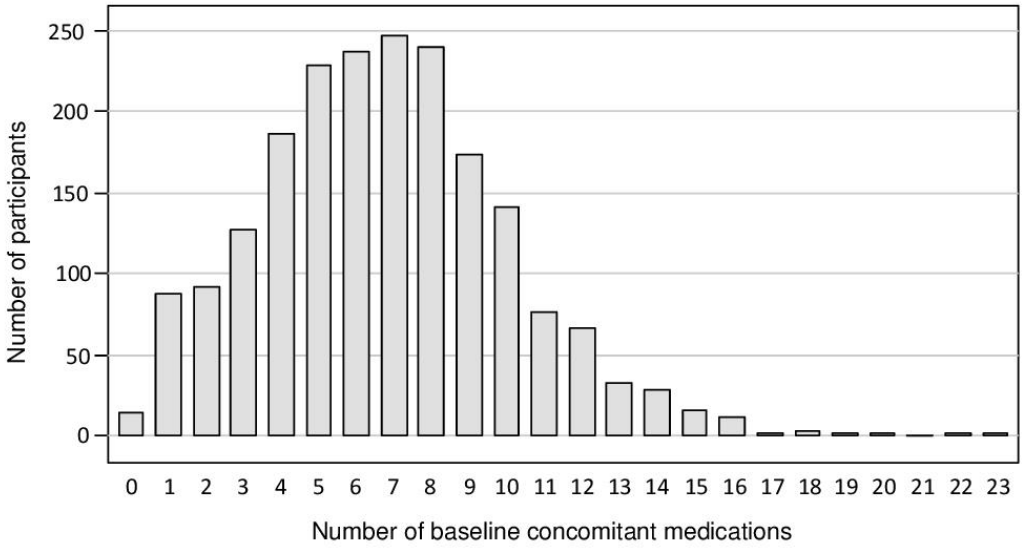
Hier darf man ruhig ind er Fussnote schreiben, was für eine Modelltechnik man verwendet hat.

Supplemental Table 5: Associations between co-medication influencing VKA metabolism and clinical outcome

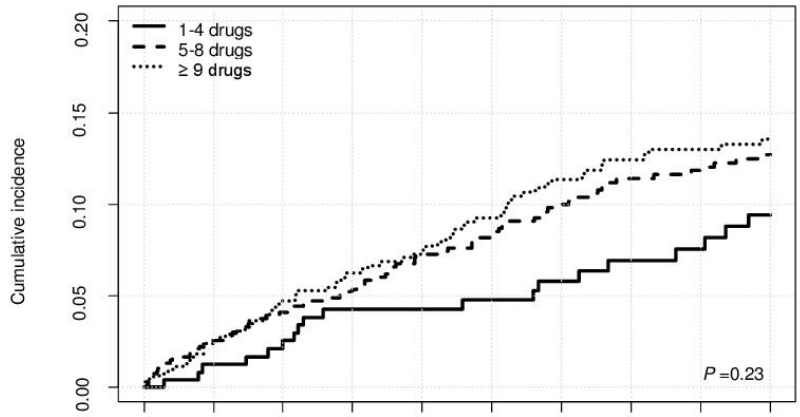
	Thromboembolic events			Clinically relevant bleeding events			Hospitalisations			All-cause mortality		
	HR	**95% CI**	**p**	**HR**	**95% CI**	**p**	**HR**	**95% CI**	**p**	**HR**	**95% CI**	**p**
Sum of co-medications that influence the INR	1.04	0.90-1.20	0.60	1.05	0.96-1.15	0.31	1.06	1.01-1.12	**0.022**	1.11	1.02-1.20	**0.012**
Sum of co-medications that increase the INR	1.02	0.86-1.21	0.84	1.03	0.92-1.16	0.56	1.07	1.00-1.14	**0.035**	1.04	0.94-1.14	0.46
Sum of co-medications that decrease the INR	1.13	0.83-1.54	0.45	1.11	0.92-1.34	0.28	1.06	0.96-1.17	0.27	1.35	1.16-1.58	**<0.001**
Sum of co-medications that increase the INR in a sample without medication that decrease the INR	1.12	0.76-1.65	0.57	1.14	0.87-1.49	0.34	1.17	1.01-1.35	**0.032**	1.10	0.82-1.48	0.53

Adjusted for age, sex, diabetes, obesity, dyslipidemia, hypertension, family history of MI/ stroke, current smoking, atrial fibrillation, chronic kidney disease, congestive heart failure, coronary artery disease, deep vein thrombosis, liver disease, myocardial infarction, pulmonary embolism, chronic lung disease, autoimmune disease

Supplemental Figure 1: Distribution of number of medication in addition to vitamin K antagonist at baseline among 2,011 participants



Supplemental Figure 2: Cumulative incidence of major bleeding stratified by number of drugs



No. at risk										
1-4 drugs	252	234	226	212	192	188	178	156	150	138
5-8 drugs	684	637	614	579	526	508	482	425	405	363
≥ 9 drugs	622	555	515	471	430	400	366	326	301	272

GENERAL DISCUSSION

This thesis investigated for the first time the link between the use of oral anticoagulants and a broad set of clinical and subclinical measures of cardiovascular disease in large observational study samples. Comprehensive analyses revealed differential effects of direct and indirect oral anticoagulant regarding cardiac structure and function as well as humoral biomarkers as intermediate phenotypes of cardiovascular disease. The findings provide new insights into pleiotropic effects of VKA and DOAC and support evidence that anticoagulant agents interact specifically with the development of cardiovascular disease in humans. This and other clinical characteristics of the patients influence the quality of oral anticoagulation therapy and make it a challenging endeavor in daily clinical practice. These essential elements should be taken into account in personalized anticoagulant therapy.

A growing body of evidence demonstrates cross-talks within the hemostatic system, but also between the hemostatic system and vasculature that occur at the level of all components of the coagulatory system including vascular endothelial cells, platelets and coagulation factors (7, 41). Thrombin- or factor Xa-mediated PAR activation on the arterial vessel wall and heart is involved in several biological processes such as vascular remodeling, leucocytes transmigration, angiogenesis, and inflammation, which contribute to atherosclerosis and atrial fibrillation (7). An interdependent relationship between hemostatic and inflammation/immune system has been intensively studied with regard to various conditions and complex diseases such as atherothrombosis (7, 42). Inflammation induces several prothrombotic conditions such as endothelial dysfunction, inhibition of anticoagulant and fibrinolytic activities as well as coagulation activation (43, 44). In addition, numerous experimental studies have also shown that hemostasis is closely related to atherogenesis (45, 46). Against this background, one might speculate that oral anticoagulation therapy might mitigate atherosclerosis. However, current data suggest that this hypothesis has two sides, and that pleiotropic effects of oral anticoagulants on the cardiovascular system depend on the type of oral anticoagulant. VKA seem to have detrimental effects on the cardiac and vascular systems, whereas DOAC appear to have rather beneficial

effects on cardiac function, lipid metabolism and atherosclerosis. Since DOAC were compared to VKA in the current analysis, it is important to note that the observed positive associations of DOAC might also be — at least in part — attributable to potential negative effects of VKA on the cardiovascular system. DOAC may also be linked to lower risks of adverse renal outcomes than VKA (47).

Knowledge of these effects will have implications for the choice of therapies for long-term anticoagulation and will help to improve long-term prophylaxis and treatment of arterial and venous thrombosis. When choosing the type of oral anticoagulant, the potential differential effect on cardiovascular risk factors and subsequent diseases may need to be taken into account. While there is first evidence that DOAC may exert cardiovascular protective effects, the currently proposed molecular mechanism for DOAC pleiotropy linking the hemostatic and cardiovascular systems needs to be further explored. It needs to be elucidated whether DOAC could have any potentially beneficial effect on the progression of cardiovascular disease. Although these analyses do not provide sufficient evidence to weigh against the use of VKA in patients susceptible to deterioration of cardiac and vascular function, first evidence was provided for potential implications of personalized antithrombotic therapy. DOAC therapy might be the most effective and safe option in high-risk groups prone to atherosclerosis. Furthermore, interactions and cross-talks between coagulation and the cardiovascular system deserve further attention of both medical experts and scientists to reveal novel, more specific and safer therapeutic targets and innovative treatment strategies.

The market launch of DOAC in addition to the established VKA has increased the complexity of antithrombotic therapy leading to numerous treatment options for physicians. The conducted survey among physicians in Rhineland-Palatinate revealed a high to very high willingness to use DOAC in everyday clinical practice. This percentage was approximately 50 % lower in the subgroup of primary care physicians compared to specialists. It can be assumed that primary care physicians were reluctant to prescribe DOAC because of skepticism towards drugs with short-term availability on the market. However, the majority of respondents did not think that VKA will completely be replaced by DOAC in the coming years. The generally high willingness to use DOAC is in line with recent reports on oral anticoagulation prescriptions. The German Drug Prescription Report 2018 recorded an increase in annual prescription from 110 million Daily Defined Dose in year 2013 to 421 million

in year 2017 (48). Also in other countries DOAC have a solid position on the market and have even taken over VKA as the more frequently prescribed oral anticoagulation (48-50). DOAC gained market share from VKA among already anticoagulated patients and especially oral anticoagulation-naive patients (51). This trend is not surprising given the advantages of DOAC. Furthermore, changes in treatment Guidelines from the European Society of Cardiology and the American College of Chest Physicians have contributed to this trend by recommending DOACs for patients with non-valvular atrial fibrillation (6, 52). In the future, total number of DOAC prescription will almost certainly increase further. Given the high number of patients with atrial fibrillation which are not on appropriate antithrombotic therapy (e.g., 20% in the GLORIA-AF registry (53)) it is important to recognize DOAC as a possible option for improving this situation. One can state that high quality of oral anticoagulation therapy is limited by the complexity of the regimens. Of note, despite the preferential use of DOAC in eligible patients with atrial fibrillation, there are still some indications which require the use of VKA (i.e., patients with mechanical heart valves) (54). The use of dabigatran in subjects with mechanical heart valves was associated with an increased risk of thromboembolic and bleeding events, as compared with warfarin, thus showing no benefit and an elevated risk (55). In addition, a previous study showed that the observed improvement in outcome of VKA-patients managed by an e-health-based coagulation service was independent of treatment quality, as assessed via TTR (32). This points to the recommendation that not only INR control should be maintained but rather that a comprehensive evaluation of the patient´s clinical characteristics (e.g., clinical status) should also be made in order to achieve optimal treatment.

Especially, elderly patients on multiple medications pose a challenge for physicians in terms of drug interactions and the decision upon anticoagulation treatment. The current analysis showed that patients with polypharmacy receiving long-acting phenprocoumon are prone to reduced treatment quality and accordingly poorer clinical outcome. This main finding is consistent with previous results on other short-acting anticoagulants like warfarin (37, 56, 57). Interestingly, patients with polypharmacy who were managed by professional anticoagulation clinics did not experience an elevated risk of hemorrhagic events (58). Therefore, it seems straightforward to suggest a service hotline and/or a specialized coagulation service to tackle difficulties regarding management of oral anticoagulation therapy in high-risk patients. Indeed, the vast majority of interviewed stakeholders advocated such

options. With regard to telephone counseling services, positive experiences have already been made in the area of heart failure therapy (59, 60). A lower rate of anticoagulation-specific and non-specific outcomes in an e-health-based specialized anticoagulation management system compared with regular medical care for patients with VKA has been demonstrated in previous studies (32). This supports the hypothesis that a specialized individually tailored healthcare model (i.e., organized standardized care, detailed standardized assessment of clinical status at each visit, and individualized termination of the control visits depending on the perceived medical necessity) allows for early identification and treatment of evolving health problems. Against this background, treatment of patients on multiple medications seems a plausible alternative to regular medical care in order to achieve better treatment quality and corresponding clinical outcome. There is evidence that in the setting of patients with non-valvular atrial fibrillation and polypharmacy, DOAC seem an effective and safe alternative to VKA (56, 61-63). This suggests that patients on multiple medications should rather be treated with DOAC than VKA. However, to achieve individualization of anticoagulation treatment more research is required in this respect.

Strengths and limitations

For all analyses described in this thesis observational data were used. The Gutenberg Health Study and MyoVasc Study are both unique regarding overall number of participants and highly standardized deep clinical phenotyping comprising a 5-h clinical investigation (e.g., ECG, 2D-, and 3D-cardiac echocardiography, sonography of the carotid artery, and assessment of vascular function) and comprehensive blood withdrawal for biobanking (exceeding the setting of clinical studies). This allowed investigating the associations of VKA and DOAC on subclinical cardiovascular parameters in a real-world setting. Up to now, there are no studies that have assessed (sub)clinical phenotypes in this level of detail. The evaluation of surrogate markers of intermediate disease phenotypes instead of clinical endpoints offered the opportunity to gain pathomechanistic insights in the course of the disease. The prospective design of all studies opened up the possibility of investigating time-dependent associations, although not for all studies follow-up data were available at the time of analysis (i.e., Gutenberg Health Study and MyoVasc Study). The cross-sectional design of those studies warrants caution when interpreting the results in a causal manner. Therefore, studies covering an adequate period of exposure to VKA

or DOAC to analyze the effects on atherosclerosis over time should follow after these investigations. It is important to critically appraise this research against the Bradford-Hill criteria for causality, to determine the strength of evidence for a causal relationship. For the thrombEVAL study, follow-up data were available which allowed analyses of incident adverse events during VKA therapy. Importantly, information on outcome events were validated by source data (e.g., medical records) and subsequently adjudicated by a clinical events committee, guaranteeing high quality of outcome assessment. Although evidence for differential effects among DOAC subgroups with regard to onset and course of cardiovascular disease could not be provided, it cannot be excluded that specific inhibition of factor IIa and Xa may exert differential effects on the cardiovascular system in humans. This remains to be evaluated in future investigations. Due to the observational nature of the study, exposure to VKA or DOAC has not been allocated randomly, which might limit the interpretability. Differences of clinical characteristics between groups (i.e., VKA users vs non-users; DOAC vs. VKA users) have been addressed with advanced statistical methods. Multivariate regression analysis, propensity score weighting and specific subgroup analyses were applied to address confounding and to confirm the robustness and validity of results. Based on the participation rate in the survey among clinicians, which is expectedly low in medical surveys (64), results may be impacted by response bias (e.g., over- or under-representation of individual groups). It can be assumed that the majority of physicians did not feel addressed by the specific topic. Moreover, only physicians took part that were particularly interested in the subject or had concerns about it. Results may only be limitedly extrapolated to the underlying populations and should be interpreted with caution.

Conclusion

The investigations included in this dissertation have demonstrated that oral anticoagulation drugs affect the development and course of subclinical parameters of cardiovascular disease differentially. Inhibition of coagulation proteases not only reduces clot formation to exert its protective role, but also influences pathophysiological processes relevant for the development and progression of atherosclerosis. These are important results that improve our current understanding of clinical implications of long-term oral anticoagulation treatment regarding potential vascular and cardiac side effects. Treatment with oral anticoagulants in daily clinical practice remains challenging due to its potential effects on the cardiovascular system

and the impact of the concomitant clinical situation with factors such as polypharmacy. Gaining further knowledge on these effects may help to develop concepts of individualized anticoagulation therapy. Specialized care models might facilitate optimized oral anticoagulation therapy and might be of substantial value in special patient populations.

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APPENDIX

Aus Datenschutzgründen gelöscht

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“ Zwei Dinge sind zu unserer Arbeit nötig: Unermüdliche Ausdauer und die Bereitschaft, etwas, in das man viel Zeit und Arbeit gesteckt hat, wieder wegzuwerfen.”

— Albert Einstein —

LIST OF PUBLICATIONS

Original peer-reviewed articles as first author

Eggebrecht L, Nagler M, Göbel S, Lamparter H, Keller K, Wagner B, Panova-Noeva M, Ten Cate V, Bickel C, Lauterbach M, Espinola-Klein C, Hardt R, Münzel T, Prochaska JH, Wild PS. Relevance of Polypharmacy for Clinical Outcome in Patients Receiving Vitamin K Antagonists. *Journal of the American Geriatric Society*. 2019;67(3):463-70

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Original peer-reviewed articles as co-author

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Panova-Noeva M, Eggebrecht L, Prochaska JP, Wild PS. Potential of multi-dimensional, large-scale biodatabases to elucidate coagulation and platelet pathways as approach towards precision medicine in thrombotic disease. Review. *Hämostaseologie*. 2019 Feb 5 [Epub ahead of print]

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PRESENTATIONS AT SCIENTIFIC MEETINGS

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Eggebrecht L, Nagler M, Göbel S, Lamparter H, Keller K, Bickel C, Lauterbach M, Espinola-Klein C, Hardt R, Münzel T, Wild PS, Prochaska JH. Polypharmacy increases the risk of adverse events in patients receiving oral anticoagulation therapy – Results from the thrombEVAL study. Internist. 2018. 59(Suppl 1): 1. p.6 - German Convention of Internists, Mannheim, Germany, 04/2018 (Oral presentation)

Eggebrecht L, Nagler M, Göbel S, Lamparter H, Keller K, Bickel C, Lauterbach M, Espinola-Klein C, Hardt R, Münzel T, Wild PS, Prochaska JH. Relevance of polypharmacy for the clinical outcome of patients receiving oral anticoagulation therapy – Results from the thrombEVAL study. Res Pract Thromb Haemost. 2017. 1(Suppl.1). - International Society on Thrombosis and Haemostasis, Berlin, Germany, 07/2017 (Poster presentations)

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Eggebrecht L, A. Schulz A, Tröbs S.-O, M. Dib M, S. Schwuchow S, Göbel S, Diestelmeier S, Arnold N, Gori T, Lackner KJ, ten Cate H, Münzel T, Prochaska JH, Wild PS. Differential effects of direct oral anticoagulants and vitamin K-antagonists on subclinical cardiovascular disease: results from the MyoVasc study. Clin Res Cardiol 106, Suppl 1, April 2017 - German Society for Cardiology, Mannheim, Germany, 03/2017 (Poster presentation)

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07 -08/ 2007	Charité – Universitätsmedizin Berlin Abteilung Kardiologie *Praktikum*

- Zusätzliche Qualifikationen

- Associate Fellow der “Research School of Translational Biomedicine” in Mainz

- Teilnahme an dem “Erasmus Summer Programme 2016” an der medizinischen Fakultät der Erasmus-Universität Rotterdam (08/2016)

- Zertifikat des Allgemeinen Promotionskollegs der Johannes Gutenberg-Universität Mainz (10/2016)

- Fremdsprachen: fließend Englisch und Grundkenntnisse in Französisch