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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': β −0.24 [−0.36/−0.12]; $P<0.0001$) and higher levels of ApoA1 (β +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' (Δ −2.36) and ApoA1 (Δ +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; Elecsys 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

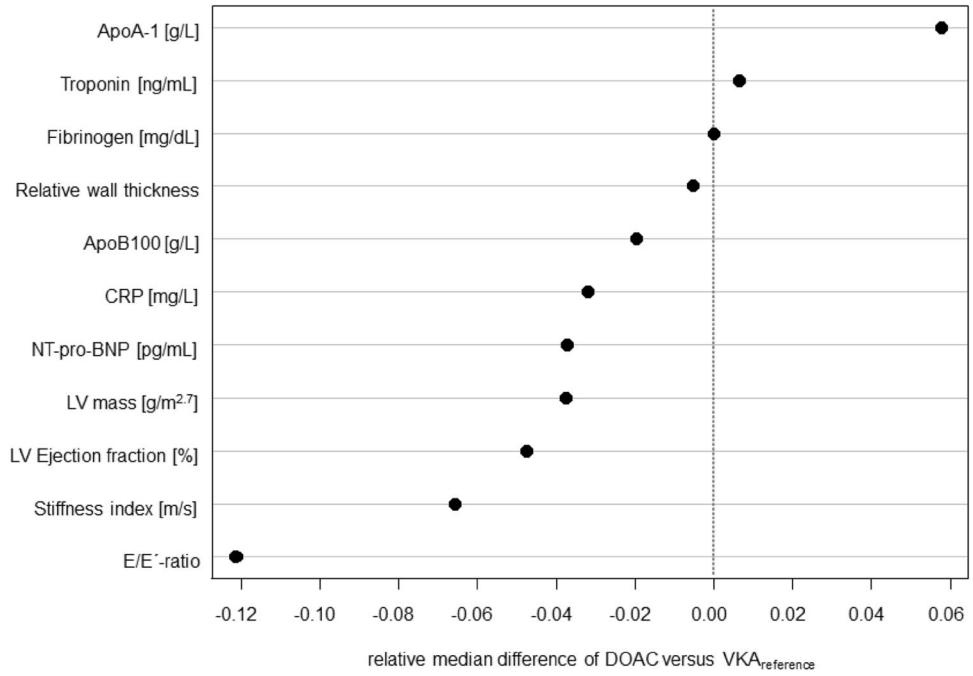

Fig. 1 Comparison of the profile of subclinical phenotypes of cardiovascular disease and inflammatory biomarkers in individuals with VKA and DOAC by propensity score-weighted analysis. Data are expressed as the relative median difference to the range between 5th and 95th percentiles. Variables are arranged 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

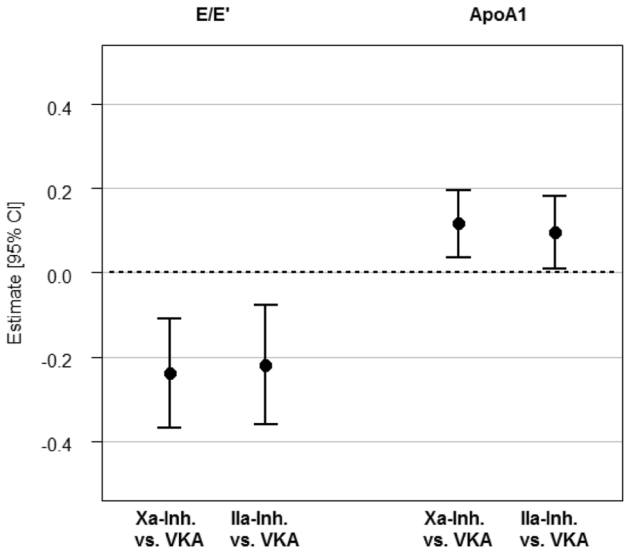

Fig. 2 Comparison of effect estimates of IIa and Xa-directed anticoagulation therapy compared to VKA therapy. The plots indicate the estimates IIa- and Xa-directed oral anticoagulation therapy on *E*/*E*′ ratio and ApoA1 in comparison with VKA therapy. The effect estimates $_{\text{DOAC vs. VKA}}$ are 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

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