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Changes in Renal Function in Patients With Atrial Fibrillation

An Analysis From the RE-LY Trial

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CME Objective for This Article: After reading this article, the reader should be able to: After reading this article, the reader should be able to: 1) understand the process of vascular calcification, dependent of matrix gla-protein, and the activation of this gla-protein, which occurs by y-carboxylation, which again is vitamin K dependent; 2) explain how vitamin K antagonism leads to vascular calcification; 3) recognize why vitamin K antagonists (VKA) might constitute a particular problem in patients with vascular disease, such as patients with chronic kidney disease; 4) discuss/find alternatives for VKA in patients already at high risk of vascular calcification, such as dialysis patients; and 5) identify the indication for non vitamin K-dependent oral anticoagulants (NOAC) and their use in atrial fibrillation (AF) patients with renal disease.

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ABSTRACT

BACKGROUND Vitamin K–dependent factors protect against vascular and renovascular calcification, and vitamin K antagonists may be associated with a decreased glomerular filtration rate (GFR).

OBJECTIVES This study analyzed changes in GFR during long-term treatment with warfarin or dabigatran etexilate (DE) in patients enrolled in the RE-LY (Randomized Evaluation of Long Term Anticoagulation Therapy) trial.

METHODS Of the 18,113 patients in the RE-LY study randomized to receive DE (110 mg or 150 mg twice daily) or warfarin, 16,490 patients with atrial fibrillation had creatinine values measured at baseline and at least 1 follow-up visit. Changes in GFR for up to 30 months were evaluated.

RESULTS GFR declined in all treatment groups. After an average of 30 months, the mean ± SE decline in GFR was significantly greater with warfarin (−3.68 ± 0.24 ml/min) compared with DE 110 mg (−2.57 ± 0.24 ml/min; $p = 0.0009$ vs. warfarin) and DE 150 mg (−2.46 ± 0.23 ml/min; $p = 0.0002$ vs. warfarin). A decrease in GFR >25% was less likely with DE 110 mg (hazard ratio: 0.81 [95% confidence interval: 0.69 to 0.96]; $p = 0.017$) or DE 150 mg (hazard ratio: 0.79 [95% confidence interval: 0.68 to 0.93]; $p = 0.0056$) than with warfarin in the observation period >18 months. Patients with poor international normalized ratio control (i.e., time in therapeutic range <65%) exhibited a faster decline in GFR. A more pronounced decline in GFR was associated with previous warfarin use and with the presence of diabetes.

CONCLUSIONS Patients with atrial fibrillation receiving oral anticoagulation exhibited a decline in renal function that was greater in those taking warfarin versus DE, and it was amplified by diabetes and previous vitamin K antagonist use. (Randomized Evaluation of Long Term Anticoagulant Therapy [RE-LY] With Dabigatran Etexilate; NCT00262600)
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Vitamin K is a hemostatic factor involved in physiological regulations beyond coagulation, including soft tissue calcification, cell growth, and apoptosis resulting in structural damage to the kidney vasculature (1). Atherosclerotic processes and vascular calcification are closely linked to the vitamin K-dependent protein matrix gamma-carboxyglutamic acid. This residue is an inhibitor of calcification, the deletion of which can produce arterial media sclerosis (2). Vitamin K antagonists (VKAs) are associated with increased calcification of renal and other arteries (1,2). Oral anticoagulation

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with VKAs has been shown to accelerate pre-existing vascular calcifications, whereas vitamin K substitution has been shown to improve these processes (3,4). VKA use is reportedly associated with increased coronary plaque load (5) and unstable plaque morphology (1). The possibility exists, therefore, that VKA treatment accelerates vascular end-organ damage, including renal dysfunction. In dialysis patients with low vitamin K levels, these mechanisms are regarded as one pathophysiologic mechanism for poor cardiovascular outcome (6,7). By contrast, thrombin antagonists such as dabigatran etexilate (DE) (8) and melagatran (9) have been shown to reduce advanced atherosclerotic plaque burden and improve endothelial function in animal models of atherosclerosis (8).

The RE-LY (Randomized Evaluation of Long Term Anticoagulation Therapy) trial database provides a unique opportunity to directly assess renal function during treatment with a VKA or a thrombin inhibitor in a moderate- to high-risk population with atrial fibrillation (AF). The present analysis compared changes in renal function in patients with AF who were assigned to receive either DE or warfarin in the RE-LY trial.

METHODS

The design, patient characteristics, and outcomes of the RE-LY trial have been published previously (10,11). The study was conducted in 967 centers in 44 countries. Patients with AF who had at least 1 additional risk factor for stroke were randomized in a 1:1:1 allocation ratio to receive DE in a blinded fashion in fixed doses of 110 mg twice daily (DE 110) or 150 mg twice daily (DE 150) or adjusted doses of warfarin (target international normalization ratio [INR]: 2.0 to 3.0) in an unblinded fashion for a median of 2 years. There was a balanced recruitment of patients previously treated with a VKA (VKA-experienced patients) and patients who had not been previously treated with a VKA (VKA-naive patients). All patients were randomized to treatment by using a central randomization service with an interactive voice response system located at the Population Health Research Institute in Hamilton, Ontario, Canada. Patients with an estimated glomerular filtration rate (GFR) ≤30 ml/min (according to the Cockcroft-Gault formula) were excluded per the protocol. Nevertheless, 90 patients with lower renal function were included.

Between December 2005 and December 2007, a total of 18,113 patients were randomized to receive DE 110 (5,983 treated), DE 150 (6,059 treated), or warfarin sodium (5,998 treated) (**Figure 1**). The study close-out was between December 2008 and March 2009. Measurement of serum creatinine (SCr) was planned at baseline; at 3, 6, and 12 months; and annually thereafter. Values were available at baseline and at least 1 post-baseline visit in 16,490 patients (n = 5,424 for DE 110; n = 5,472 for DE 150; and n = 5,594 for warfarin). For safety reasons, additional renal function testing was allowed during the study at any time; the results from these local tests, however, were not considered in this analysis. Patients taking DE who were found to have a reduced creatinine clearance (<30 ml/min) during the trial had their treatment stopped until the level increased to >30 ml/min. In cases in which the creatinine clearance level remained <30 ml/min a second time, DE was permanently discontinued for the duration of the trial, but respective patients were followed up until the trial was completed.

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration

DE = dabigatran etexilate

GFR = glomerular filtration rate

INR = international normalized ratio

SCr = serum creatinine

TTR = time in therapeutic range

VKA = vitamin K antagonist(s)

FIGURE 1 Flow Diagram of Patient Selection and Treatment Allocation

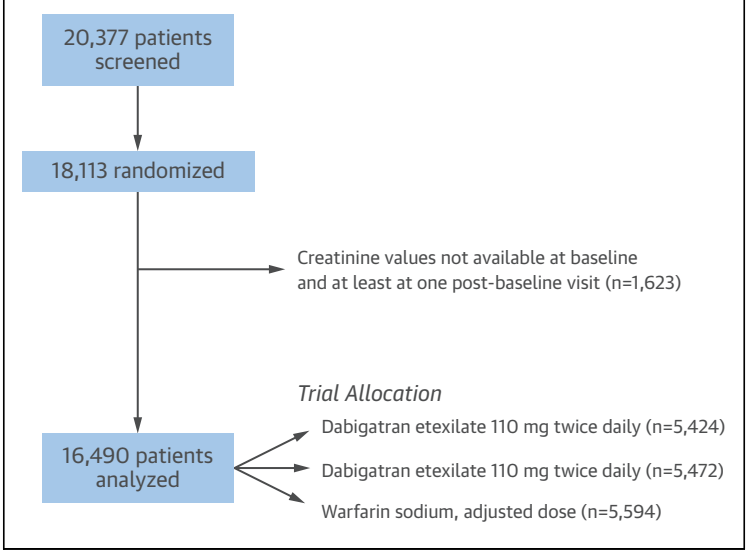


TABLE 1 Demographic Characteristics and Baseline Values

	DE 110 mg BID (n = 5,424)	DE 150 mg BID (n = 5,472)	Warfarin (n = 5,594)
Age, yrs	71.3 ± 8.6	71.3 ± 8.8	71.5 ± 8.5
Body mass index, kg/m^2	28.8 ± 5.8	28.8 ± 5.7	28.8 ± 5.7
Male	65.4	63.9	63.9
Region			
Asia	14.9	15.1	15.4
Central Europe	11.7	11.5	11.7
Western Europe	25.3	25.5	25.3
Latin America	5.4	5.4	5.2
United States, Canada	36.9	37.0	36.7
Other	5.7	5.6	5.7
AF type			
Paroxysmal	32.0	32.7	33.5
Permanent	35.3	35.7	34.1
Persistent	32.6	31.6	32.4
$CHADS_2$ score			
0–1	32.9	32.6	31.4
2	34.9	35.3	36.7
3–6	32.2	32.1	32.0
GFR (CKD-EPI)	65.8 ± 16.7	65.8 ± 17.0	66.0 ± 16.5
CKD stages			
1 (≥90 ml/min)	7.5	8.1	7.2
2 (60 to <90 ml/min)	55.4	53.9	55.6
3 (30 to <60 ml/min)	36.2	37.1	36.4
4–5 (<30 ml/min)	0.9	0.8	0.7
History of stroke/SEE/TIA	21.6	22.5	21.6
History of myocardial infarction	16.2	16.9	15.9
History of heart failure	31.8	31.8	31.5
Documented coronary artery disease	27.3	28.0	27.5
Hypertension requiring medical treatment	78.8	78.8	78.6
History of diabetes mellitus	23.5	22.8	23.2

Continued on the next page

Individual observation periods ranged between 12 and 37 months. Patients were subdivided into 3 groups depending on their time of recruitment and their resulting ability to have the last SCr measurement recorded at 12 and 24 months after randomization or later. The majority of measurements beyond 24 months occurred at ~30 months. Measurements were allocated to time points according to the following schedule: 3 months, <137 days; 6 months, 137 to 273 days; 12 months, 274 to 547 days; 24 months, 548 to 821 days; and 30 months, ≥822 days. If >1 value per time window was available, the value closest to the center of the respective interval was selected for analysis.

MEASUREMENT OF RENAL FUNCTION. Venous blood was drawn at randomization, before initiation of study treatment, and at all visits that included a protocol-driven SCr assessment. The blood was centrifuged within 30 min at 2,000 g for 10 min. The tubes were thereafter immediately frozen at -20°C or colder. Aliquots were stored centrally at -70°C to allow for batch analysis. Plasma creatinine measurements were performed in a core laboratory by using a Roche Modular analyzer with a kinetic colorimetric compensated Jaffe assay (Roche Modular, Meylan, France).

GFR was estimated from SCr (12,13), and the following equations were used. Cockcroft-Gault equation: GFR [ml/min] = ([140 - age (years)] × [weight (kg)] × 0.85 [if female]/[72 × SCr (mg/dl)]); Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation: $GFR = 141 \times \min(SCr\ [mg/dl]/k,1)^{\alpha} \times \max(SCr\ [mg/dl]/k, 1)^{-1.209} \times 0.993^{age}$ [years] × 1.018 (if female) × 1.159 (if black), in which k is 0.7 for female subjects and 0.9 for male subjects, and α is -0.329 for female subjects and -0.411 for male subjects. For sensitivity analyses, GFR was also estimated according to the Modification of Diet in Renal Disease equation by using the following formula: $GFR\ [ml/min] = 186 \times SCr\ [mg/dl]^{-1.154} \times age\ [years]^{-0.203} \times 1.21$ (if black) × 0.742 (if female). Estimation of GFR with the CKD-EPI equation produced the smallest variation (coefficient of variation ~25%), whereas the Cockcroft-Gault formula produced the highest (coefficient of variation ~37%). Because the most precise estimation of renal function and the related changes seemed to occur with CKD-EPI, the results regarding renal function decline are given for GFR determined by using this equation.

STATISTICAL ANALYSIS. This study was a post-hoc analysis. Continuous variables at baseline are presented as mean ± SD, with between-group comparisons tested by using an analysis of variance. Adjusted means (i.e., estimates resulting from model-based analyses) are reported together with respective SEs. Categorical variables are presented as percentages and were compared by using chi-square tests.

Mean changes from baseline over time were analyzed by using a restricted maximum likelihood-based repeated measures approach (14). Analyses included the fixed effects of treatment, time point, time of recruitment (early, intermediate, or late; determining the ability to reach the 12-, 24-, or 30-month visit), and treatment-by-time-point interaction, as well as the continuous, fixed covariates of baseline and baseline-by-time-point interaction. An unstructured (co)variance was used to model the within-patient measurements, and the Kenward-Roger approximation was used to estimate the denominator degrees of freedom. To protect against spurious findings, we implemented the following procedure for the comparison of treatment groups: in case of a significant treatment-by-time interaction (an alpha level of 0.05), homogeneity of treatments at each time point was tested at an alpha level of

0.01 (Bonferroni correction to adjust for multiplicity); in all analyses in which the 2 DE doses were evaluated individually at time points when treatments were significantly heterogeneous, the 2 doses were tested against warfarin at an alpha level of 0.01/2 = 0.005. Subgroup analyses were performed for diabetes and previous use of VKA treatment. In addition, as a form of sensitivity analysis, the time to first substantial deterioration of renal function was determined for each patient, defined as a reduction in GFR by at least 25% (first RIFLE criterion); this cutoff was deliberately used although it was developed by using data from patients with acute kidney injury (15). A similar analysis was performed by using a 30% decline in GFR because this decline within 2 to 3 years was shown to be predictive of end-stage renal disease occurring later (16,17). These data were analyzed by applying Cox regression with a separation of time on treatment, using a cutoff of 18 months. All analyses were performed by using SAS version 9.2 (SAS Institute, Inc., Cary, North Carolina).

RESULTS

BASELINE CHARACTERISTICS. Baseline characteristics for the DE groups and warfarin are displayed in Table 1. Baseline characteristics were similar between patients recruited early, during the intermediate phase, or late into the trial, which determined ability to reach visits at 24 or 30 months. The risk profiles of patients were comparable, independent of whether they were recruited early or late. Online Table 1 summarizes the baseline renal parameters in the 3 treatment arms. Renal parameters at baseline were similar among the treatment groups and did not differ when patients were grouped according to their time of recruitment. Moderate renal impairment (creatinine clearance according to the Cockcroft-Gault formula of 30 to <50 ml/min) was present at baseline in 18.6% of all patients, 36.6% who were in chronic kidney disease stage 3 (based on the CKD-EPI equation).

GFR CHANGES FROM BASELINE OVER TIME. A continuous decline in kidney function was observed in the total patient population. Table 2 displays the adjusted changes from baseline in GFR (based on the CKD-EPI equation), using the model for repeated measurements as described in the Methods but without any treatment-related factors. From the mean reductions at each time point, respective annual reductions were calculated. The calculated annual rate of decline was larger when only the early measurements were considered but was less apparent when the complete time span was taken into consideration. The decline was more prominent in patients with previous VKA use (especially in the beginning of the trial) and in patients with diabetes (especially toward the end of the trial). It is also noteworthy that the baseline values were lower in patients with previous VKA use compared with those who were treatment naive and in patients with diabetes versus those without diabetes. Previous VKA use was part of the randomization strategy (10).

TABLE 1 Continued

	DE 110 mg BID (n = 5,424)	DE 150 mg BID (n = 5,472)	Warfarin (n = 5,594)
Previous VKA use (stratified randomization)			
Naive	49.5	49.5	50.5
Experienced	50.5	50.5	49.5
Duration of previous use of VKA, months			
Median	3.0	3.0	2.0
Q1–Q3	0.0–30.0	0.0–31.0	0.0–28.0
Smoking			
Ex-smoker	44.4	43.9	43.4
Nonsmoker	48.2	48.5	49.2
Smoker	7.4	7.6	7.4
Alcohol consumption	34.1	33.6	33.5
Normal study termination	91.7	91.7	90.5
Concomitant medication (>10%)			
Beta-blocker	63.4	64.1	62.0
Diuretic	50.5	51.2	50.7
ACE inhibitors	45.2	45.4	44.2
Statin	45.4	44.5	44.8
ASA	39.8	38.8	40.3
Calcium-channel blocker	33.0	32.1	32.6
Digoxin	29.6	28.5	29.4
P-gp inhibitor	24.3	24.2	24.2
ARBs	24.2	24.2	23.8
Vitamins	22.0	21.6	20.6
Oral hypoglycemic	17.0	16.7	16.5
Proton pump inhibitor	14.3	14.0	13.8
Alpha-blocker/other vasodilator	13.1	13.0	13.4
Amiodarone	10.5	11.0	10.6

Values are mean ± SD or %.

ACE = angiotensin-converting enzyme; AF = atrial fibrillation; ARBs = angiotensin receptor blockers; ASA = aspirin; BID = twice daily; $CHADS_2$ = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, and stroke/TIA; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; DE = dabigatran etexilate; GFR = glomerular filtration rate; P-gp = P-glycoprotein 1; Q = quartile; SEE = systemic embolic event; TIA = transient ischemic attack; VKA = vitamin K antagonist.

GFR CHANGES FROM BASELINE OVER TIME ACCORDING TO TREATMENT GROUP. Table 3 and Figure 2 summarize the main results of GFR changes from baseline according to treatment group. There was a significant treatment-by-time-point interaction ($p < 0.0001$), indicating that there were differences between treatment groups which differed between time points. Early after 3 months, the greater decrease in GFR with both DE doses was nominally (at a $p < 0.05$ level) statistically significant for DE 150 versus warfarin ($p = 0.022$), although it did not maintain significance after Bonferroni correction. Although

TABLE 2 Mean Baseline Values of Estimated GFR (CKD-EPI) and Adjusted* Mean Changes From Baseline in All Patients and According to Previous VKA Use and Diabetes Status

		Previous VKA Use		Diabetes	
	All Patients	No	Yes	No	Yes
Baseline					
N	16,490	8,219	8,269	12,672	3,818
Mean ± SE	65.87 ± 0.13	66.13 ± 0.18	65.61 ± 0.18	66.34 ± 0.15	64.33 ± 0.29
3 months					
N	15,544	7,717	7,825	11,973	3,571
Adjusted mean ± SE change from baseline	-0.97 ± 0.08	-0.64 ± 0.11	-1.29 ± 0.10	-0.97 ± 0.09	-0.99 ± 0.17
p Value (vs. previous time point)	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Calculated annual decline, mean ± SE	-3.89 ± 0.31	-2.56 ± 0.46	-5.18 ± 0.41	-3.87 ± 0.35	-3.95 ± 0.66
6 months					
N	15,151	7,496	7,654	11,663	3,488
Adjusted mean ± SE change from baseline	-1.18 ± 0.08	-1.10 ± 0.12	-1.25 ± 0.11	-1.11 ± 0.09	-1.38 ± 0.18
p Value (vs. previous time point)	0.0084	< 0.0001	0.64	0.084	0.025
Calculated annual decline, mean ± SE	-2.35 ± 0.17	-2.20 ± 0.25	-4.98 ± 0.22	-2.23 ± 0.18	-2.76 ± 0.37
12 months					
N	14,277	6,986	7,290	11,022	3,255
Adjusted mean ± SE change from baseline	-1.87 ± 0.09	-1.66 ± 0.13	-2.06 ± 0.14	-1.73 ± 0.10	-2.34 ± 0.20
p Value (vs. previous time point)	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Calculated annual decline, mean ± SE	-1.87 ± 0.09	-1.66 ± 0.13	-2.06 ± 0.14	-1.73 ± 0.10	-2.34 ± 0.20
24 months					
N	10,321	4,934	5,386	7,998	2,323
Adjusted mean ± SE change from baseline	-2.60 ± 0.11	-2.18 ± 0.16	-2.98 ± 0.14	-2.31 ± 0.12	-3.56 ± 0.23
p Value (vs. previous time point)	<0.0001	0.0003	<0.0001	<0.0001	<0.0001
Calculated annual decline, mean ± SE	-1.30 ± 0.05	-1.09 ± 0.08	-1.49 ± 0.07	-1.16 ± 0.06	-1.78 ± 0.12
30 months					
N	5,060	1,859	3,200	3,905	1,155
Adjusted mean ± SE change from baseline	-2.91 ± 0.14	-2.52 ± 0.22	-3.24 ± 0.22	-2.53 ± 0.15	-4.27 ± 0.30
p Value (vs. previous time point)	0.014	0.10	0.11	0.13	0.0091
Calculated annual decline, mean ± SE	-1.16 ± 0.05	-1.01 ± 0.09	-1.30 ± 0.07	-1.01 ± 0.06	-1.71 ± 0.12

*Statistical model includes continuous baseline, month, baseline-by-month interaction, and patient cohort (early, intermediate, and late recruitment).
Abbreviations as in Table 1.

there were similar reductions between the treatment arms after 6 and 12 months, the reductions with DE treatments were smaller after 30 months compared with warfarin (DE 110: -2.57 [p = 0.0009 vs. warfarin]; DE 150: -2.46 [p = 0.0002 vs. warfarin]; and warfarin: -3.68). These results were confirmed in sensitivity analyses: 1) including only patients who did not discontinue the study early (91.3%); 2) including only patients who were recruited early and were therefore able to reach the 30-month visit; and 3) by using multiple imputation and "simple" analysis of covariance models according to time point. The results in those patients recruited early and who were able to reach the 30-month visit were similar and are summarized in **Table 4** (Online Figure 1). The results were also confirmed when at least 2, 3, 4, or 5 GFR values required during follow-up were available for analysis or when the Modification of Diet in Renal Disease equation was used for estimation of GFR.

A multivariate model that included age, sex, ethnicity, region, smoking, alcohol consumption, AF type, pre-treatment with VKA, history of diabetes, stroke/systemic embolic event/transient ischemic attack, hypertension, coronary artery disease, heart failure, myocardial infarction, and the most frequent co-medications (**Table 1**) as additional explanatory variables determined virtually the same results with regard to differences between treatment groups. Among the explanatory variables, age, sex, history of myocardial infarction, previous VKA use, and co-medication with angiotensin receptor blockers, amiodarone, or diuretics had the strongest impact on changes in GFR ($p < 0.0001$ for all). In addition, the intention-to-treat analysis including all available data, whether on or off study medication, produced similar results. At 30 months, the decline in the group randomized to receive warfarin (-3.65) was significantly greater than in both DE groups (DE 110: -2.69, p = 0.0032; DE 150: -2.62, p = 0.0014). To address the potential concern that patients in the 2 DE groups had stopped the trial early due to greater renal function deterioration (and therefore a positive selection is

responsible for the better outcomes at later time points), the mean baseline, last value, and change from baseline were evaluated for CKD-EPI, creatinine clearance, and SCr in all patients with early study termination. No major differences were seen between treatment groups. The number of patients with creatinine clearance <30 ml/min at the time of stopping totaled 22, 34, and 25 in the 3 treatment groups, respectively. These numbers are comparable and are not high enough to explain the differences between treatments.

GFR CHANGES FROM BASELINE OVER TIME ACCORDING TO LEVEL OF INR CONTROL. Figure 3 (left panel) displays GFR changes in the DE groups compared with warfarin at different levels of INR control. Patients on warfarin who were in the therapeutic range (INR 2.0 to 3.0) for <65% of the time had a significantly larger decline in GFR at 24 and 30 months compared with those receiving both DE doses ($p < 0.005$ for all). To explore whether this finding is related to vitamin K antagonism, we divided the warfarin group into 4 subgroups. Information on INR was missing for 24 patients (0.4%). The 4 subgroups were: 1) patients with "excellent" INR control (time in therapeutic range [TTR] ≥80%, n = 1,236 [22.1%]); 2) patients with "good" INR control (TTR ≥65% to <80%, n = 1,889 [33.8%]); 3) patients with "poor" INR control (TTR <65%) and INR predominantly below the therapeutic range (TTR <65%, n = 1,725 [30.8%]); and 4) patients with "poor" INR control and INR predominantly above the therapeutic range (n = 720 [12.9%]). Both DE doses were associated with smaller GFR reductions that were significant at 12 and 24 months compared with the group of overdosed warfarin patients (i.e., those at an INR level predominantly above the therapeutic range [INR mainly >3.0]; $p < 0.005$ for all) (Figure 3, right panel). Patients who were overdosed with warfarin had a more prominent decline in GFR than those in the targeted range or those undertreated (INR mainly <2.0) with warfarin (Figure 4). These differences regarding the INR control levels were not observed for absolute doses of warfarin taken (not shown).

GFR CHANGES FROM BASELINE OVER TIME ACCORDING TO DIABETES STATUS. We determined whether subjects with a high risk of progressive decline in renal function, such as patients with diabetes, experienced differential effects with DE or warfarin. Because only minor differences were observed between the 2 DE doses in the main analysis, all patients assigned to DE were pooled. Figure 5 depicts the decline in patients with and without diabetes. In general, patients with diabetes had lower GFR levels at baseline compared with nondiabetic subjects (64.3 vs. 66.3 ml/min, $p < 0.0001$; 64.0 vs. 66.4 ml/min, $p < 0.0001$ [after adjustment]) and had a more pronounced GFR decline. At 30 months, the decline in GFR in patients with diabetes was significantly greater with warfarin compared with DE ($p < 0.005$).

TABLE 3 Mean Baseline Values of Estimated GFR (CKD-EPI) and Adjusted* Mean Changes From Baseline by Treatment

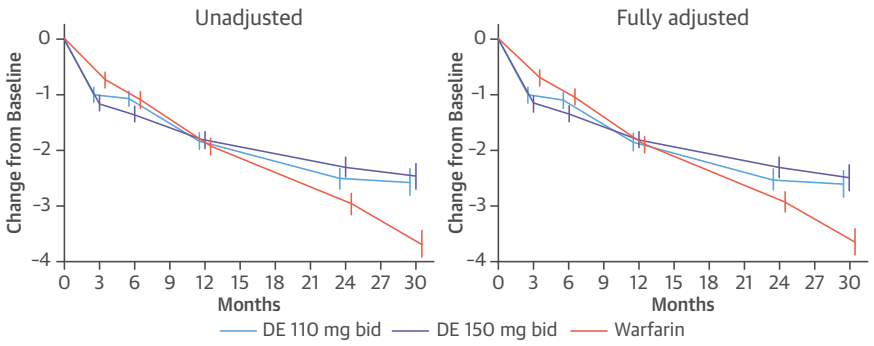
	DE 110 mg BID	DE 150 mg BID	Warfarin
Baseline			
N	5,424	5,472	5,594
Mean ± SE	65.81 ± 0.23	65.77 ± 0.23	66.04 ± 0.22
3 months			
N	5,130	5,171	5,243
Adjusted mean ± SE change from baseline	-1.01 ± 0.13	-1.17 ± 0.14	-0.74 ± 0.13
Difference vs. warfarin, mean ± SE	-0.27 ± 0.19	-0.43 ± 0.19	
p Value	0.15	0.022	
6 months			
N	5,000	5,005	5,146
Adjusted mean ± SE change from baseline	-1.08 ± 0.14	-1.35 ± 0.14	-1.10 ± 0.14
Difference vs. warfarin, mean ± SE	0.02 ± 0.20	-0.26 ± 0.20	
p Value	0.93	0.21	
12 months			
N	4,686	4,696	4,895
Adjusted mean ± SE change from baseline	-1.84 ± 0.15	-1.82 ± 0.15	-1.94 ± 0.15
Difference vs. warfarin, mean ± SE	0.10± 0.22	0.12 ± 0.22	
p Value	0.63	0.59	
24 months			
N	3,368	3,434	3,519
Adjusted mean ± SE change from baseline	-2.51 ± 0.18	-2.31 ± 0.18	-2.96 ± 0.18
Difference vs. warfarin, mean ± SE	0.45 ± 0.26	0.65 ± 0.26	
p Value	0.081	0.011	
30 months			
N	1,672	1,685	1,703
Adjusted mean ± SE change from baseline	-2.57 ± 0.24	-2.46 ± 0.23	-3.68 ± 0.24
Difference vs. warfarin, mean ± SE	1.11 ± 0.33	1.22 ± 0.33	
p Value	**0.0009**	**0.0002**	

The p value for treatment-by-month interaction was <0.0001. The p values for test of treatment differences according to month were: 0.068 (3 months), 0.32 (6 months), 0.84 (12 months), 0.035 (24 months), and 0.0003 (30 months). Significant p values (after adjustment for multiplicity of testing) are given in **bold**. *Statistical model includes treatment, continuous baseline, month, baseline-by-month interaction, treatment-by-month interaction, and patient cohort (early, intermediate, and late recruitment).

Abbreviations as in Table 1.

GFR CHANGES FROM BASELINE OVER TIME ACCORDING TO PREVIOUS USE OF VKA. VKA-experienced patients had slightly lower GFR values at baseline compared with VKA-naive patients (65.6 vs. 66.1 ml/min; $p = 0.046$), but after adjustment, this difference vanished (65.8 vs. 65.9 ml/min; $p = 0.69$). Figure 6 depicts the decline in VKA-experienced and VKA-naive patients over time. In general, experienced patients had a more pronounced GFR decline than naive patients. In the first year, there was little difference between DE and warfarin in either subgroup. Later, however, patients taking DE had a smaller GFR reduction (difference compared with warfarin in VKA-naive patients at 24 months: 1.03 [$p = 0.0011$];

FIGURE 2 Estimated GFR (CKD-EPI) Over Time



Data are shown **(left)** unadjusted and **(right)** fully adjusted for age, sex, ethnicity regions, smoking, alcohol consumption, atrial fibrillation type, history of diabetes, stroke, embolism, transient ischemic attack, hypertension, coronary artery disease, heart failure, myocardial infarction, previous vitamin K antagonist use, and most frequent concomitant medications. bid = twice daily; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; DE = dabigatran etexilate.

TABLE 4 Mean Baseline Values of Estimated GFR (CKD-EPI) and Adjusted* Mean Changes From Baseline by Treatment, Analysis Including Only Patients Who Were Recruited Early and Were Therefore Able to Reach the 30-Month Visit

	DE 110 mg BID	DE 150 mg BID	Warfarin
Baseline			
N	2,257	2,277	2,311
Mean ± SE	65.53 ± 0.35	65.08 ± 0.35	65.46 ± 0.33
3 months			
N	2,089	2,111	2,138
Adjusted mean ± SE change from baseline	-0.98 ± 0.20	-1.00 ± 0.20	-0.52 ± 0.20
Difference to warfarin, mean ± SE	-0.46 ± 0.29	-0.48 ± 0.29	
p Value	0.11	0.094	
6 months			
N	2,080	2,059	2,125
Adjusted mean ± SE change from baseline	-0.34 ± 0.21	-0.61 ± 0.21	-0.49 ± 0.22
Difference to warfarin, mean ± SE	0.15 ± 0.30	-0.11 ± 0.30	
p Value	0.62	0.70	
12 months			
N	2,020	2,010	2,096
Adjusted mean ± SE change from baseline	-1.90 ± 0.22	-2.01 ± 0.23	-1.77 ± 0.22
Difference to warfarin, mean ± SE	-0.13 ± 0.31	-0.24 ± 0.32	
p Value	0.69	0.45	
24 months			
N	1,669	1,668	1,718
Adjusted mean ± SE change from baseline	-2.69 ± 0.26	-2.76 ± 0.26	-3.28 ± 0.26
Difference to warfarin, mean ± SE	0.59 ± 0.37	0.52 ± 0.37	
p Value	0.11	0.16	
30 months			
N	1,672	1,685	1,703
Adjusted mean ± SE change from baseline	-2.53 ± 0.27	-2.55 ± 0.26	-3.66 ± 0.27
Difference to warfarin, mean ± SE	1.12 ± 0.38	1.10 ± 0.37	
p Value	**0.0029**	**0.0032**	

*Statistical model includes treatment, continuous baseline, month, baseline-by-month interaction, treatment-by-month interaction. The p value for treatment-by-month interaction was 0.0006. The p values for test of treatment differences according to month were: 0.16 (3 months), 0.67 (6 months), 0.75 (12 months), 0.22 (24 months), and 0.0031 (30 months). Significant p values (after adjustment for multiplicity of testing) are given in **bold**.

Abbreviations as in Table 1.

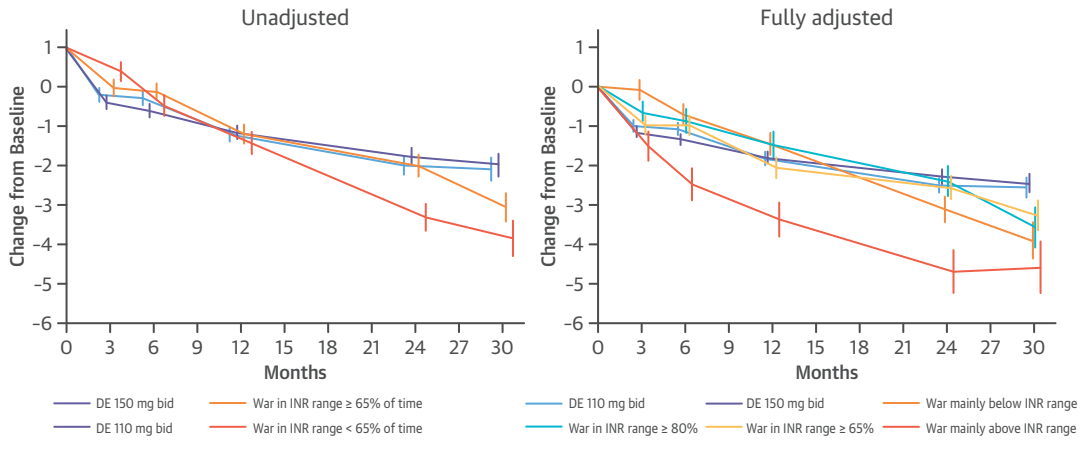
difference compared with warfarin in VKA-experienced patients at 30 months: 1.07 [p = 0.0035]).

TIME TO FIRST SUBSTANTIAL DETERIORATION IN RENAL FUNCTION. The rates of substantial deterioration in renal function (>25% decline in CKD-EPI) by time were investigated for the 3 treatment groups. Cox regression analysis with study period (initial 18 months vs. later) as an additional factor confirmed higher deterioration rates in the second half of the trial with warfarin. For the treatment-by-period interaction, the resulting p value was 0.038, indicating that there may be a differential treatment effect in both study periods. Although no treatment differences were seen in the first 18 months, there was an advantage of both DE doses over warfarin later in the period (hazard ratio: 0.81 [95% confidence interval (CI): 0.69 to 0.96]; p = 0.017 for DE110 vs. warfarin; hazard ratio: 0.79 [95% CI: 0.68 to 0.93]; p = 0.0056 for DE150 vs. warfarin). A cutoff of 25% was chosen, which refers to an established RIFLE criterion (15) for acute kidney failure. Because a decline in GFR over 2 to 3 years is reportedly predictive of the development of end-stage renal disease, a cutoff of 30% was also investigated (16,17). After 18 months, the decline in GFR was less for DE 110 (hazard ratio: 0.75 [95% CI: 0.62 to 0.92]; p = 0.00052), and DE 150 (hazard ratio: 0.66 [95% CI: 0.54 to 0.81]; p ≤ 0.0001) compared with warfarin.

DISCUSSION

Comparing DE 110 and DE 150 versus warfarin in this post-hoc analysis from the RELY trial, a significant treatment-by-time interaction was observed, with a

FIGURE 3 Estimated GFR (CKD-EPI) Over Time by INR Control

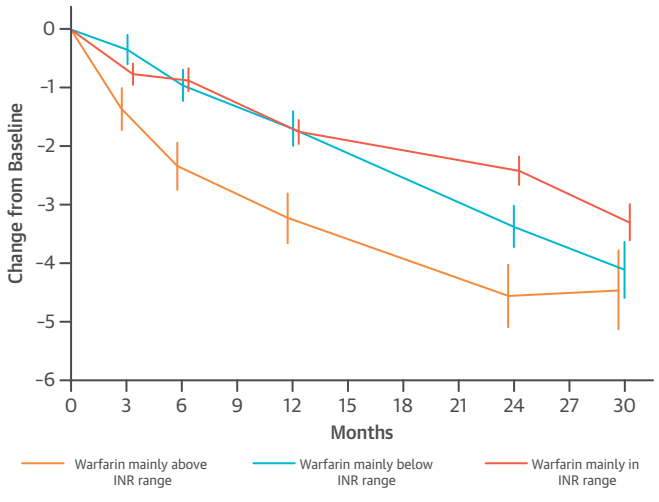


Data are shown **(left)** unadjusted and **(right)** fully adjusted for age, sex, ethnicity regions, smoking, alcohol consumption, atrial fibrillation type, history of diabetes, stroke, embolism, transient ischemic attack, hypertension, coronary artery disease, heart failure, myocardial infarction, previous vitamin K antagonist use, and most frequent concomitant medications. INR = international normalized ratio (target range 2.0–3.0); War = warfarin; other abbreviations as in Figure 2.

trend toward a larger earlier decline in renal function with DE (150-mg dose only) and a larger late decline with warfarin. The decline in GFR as determined by using the CKD-EPI equation was limited to ~1 ml/min per year, although this outcome was more pronounced with warfarin than with DE at 30 months. Patients outside the therapeutic range of INR control (in particular those with high INR levels) and those with previous VKA treatment had a more pronounced decline, with a significantly greater reduction in GFR compared with either DE dose from 6 months onward. The GFR decline in patients with diabetes was more pronounced than in those without diabetes, whereas the difference between the warfarin and DE groups was consistent with the overall group. A continuous decline in kidney function was observed in an elderly population with AF, and the decline was most pronounced in those with diabetes (18). Compared with previous reports of annual declines in GFR in an aging population, the results observed in our analysis (annual decline of -1.15 ml/min in CKD-EPI in the overall population and -1.71 ml/min in patients with diabetes) are in agreement with these previous reports in elderly patients. This decline in renal function must be taken into consideration when administering drugs, such as DE, that are cleared by the kidney; dosing of these medications may need adjustment or treatment should be discontinued if severe renal impairment develops.

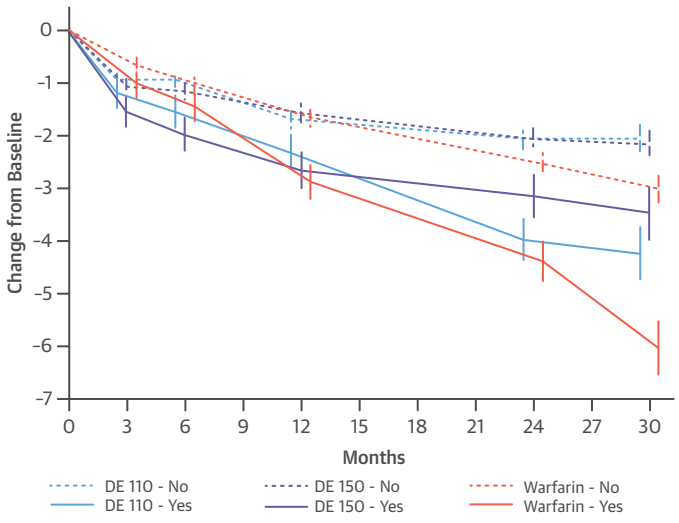
Patients with renal impairment are often high-risk cardiovascular patients with a higher prevalence of AF (19–21). Among these patients, thromboembolic complications are more prevalent than in patients with nonvalvular AF and normal renal function (22–24). When renal function is impaired, there is a variable and often clinically relevant decline in

FIGURE 4 Estimated GFR (CKD-EPI) Over Time by INR Control in Patients on Warfarin



Data adjusted for age, sex, ethnicity regions, smoking, alcohol consumption, atrial fibrillation type, history of diabetes, stroke, embolism, transient ischemic attack, hypertension, coronary artery disease, heart failure, myocardial infarction, previous vitamin K antagonist use, and most frequent concomitant medications. eGFR = estimated glomerular filtration rate; other abbreviations as in Figures 2 and 3.

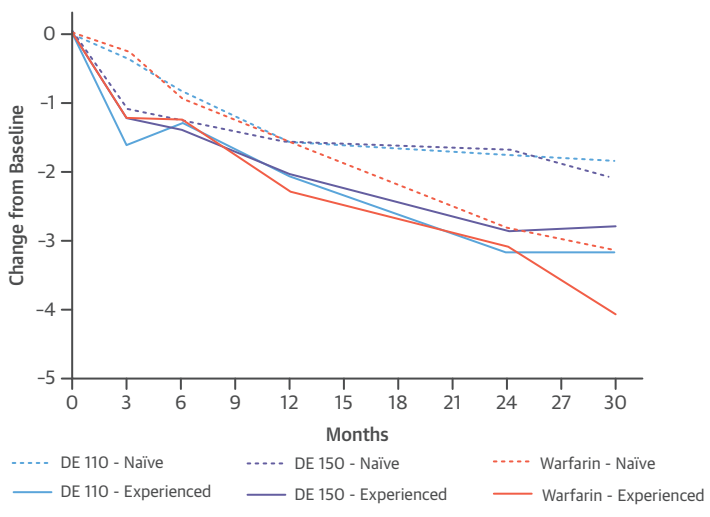
FIGURE 5 Estimated GFR (CKD-EPI) Over Time by Diabetes Status



Data adjusted for age, sex, ethnicity regions, smoking, alcohol consumption, atrial fibrillation type, history of diabetes, stroke, embolism, transient ischemic attack, hypertension, coronary artery disease, heart failure, myocardial infarction, previous vitamin K antagonist use, and most frequent concomitant medications. No = no diabetes; Yes = diabetes; other abbreviations as in Figure 2.

renal function (25) involving vascular mechanisms such as oxidative stress and inflammation and vascular calcifications, which in turn increase adverse cardiovascular outcomes (26). In AF, VKAs have been widely recommended for anticoagulation in patients with and without renal impairment (27), although many trials excluded patients with severe renal impairment (22,24). Interestingly, warfarin has been associated with biopsy-proven nephropathy in patients with and without renal impairment, which is related to increased mortality (28). These findings are in agreement with animal studies showing induction of nephropathy with high doses of warfarin (29,30).

FIGURE 6 Estimated GFR (CKD-EPI) Over Time by Previous VKA Use

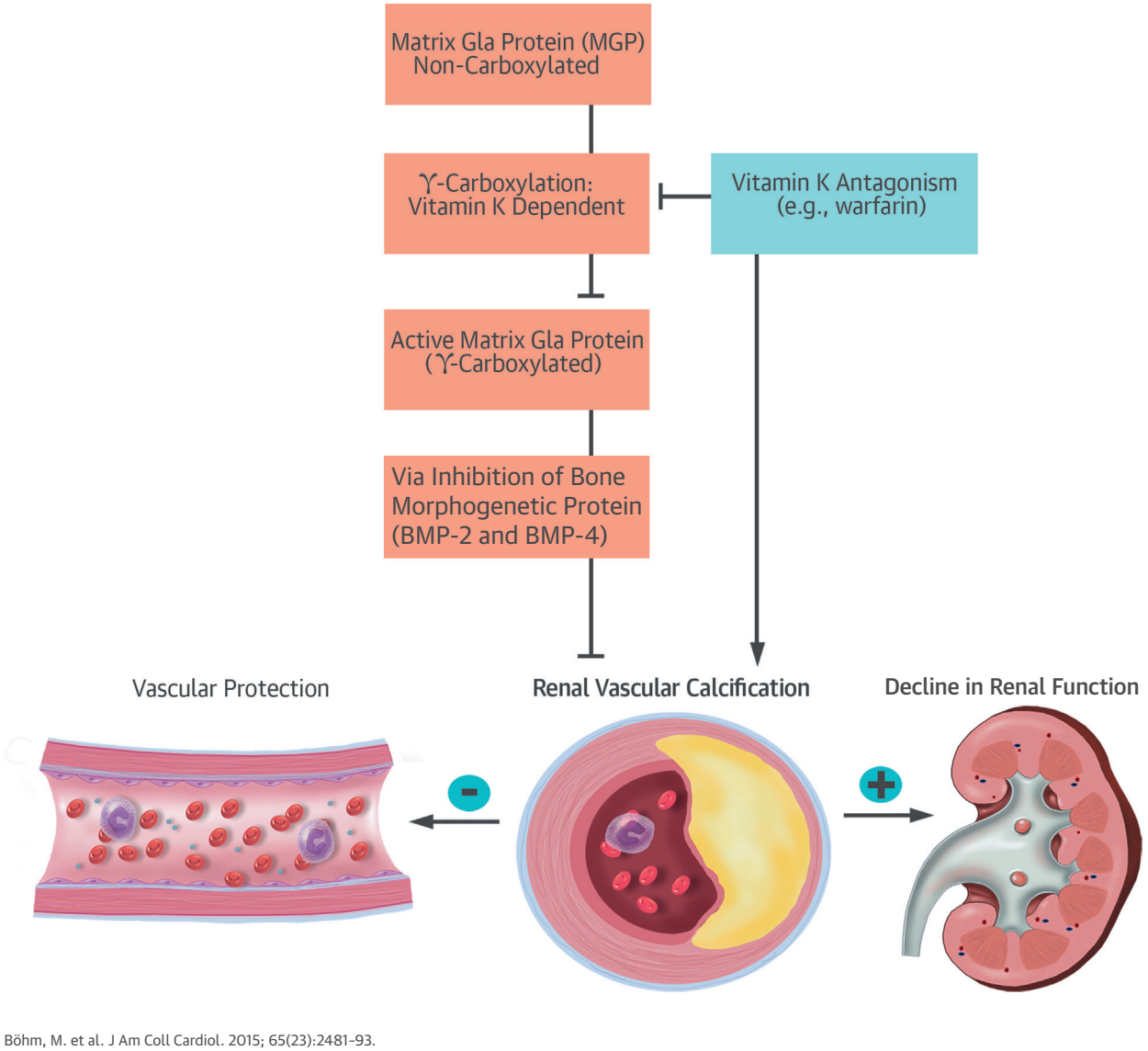


Data adjusted for age, sex, ethnicity regions, smoking, alcohol consumption, atrial fibrillation type, history of diabetes, stroke, embolism, transient ischemic attack, hypertension, coronary artery disease, heart failure, myocardial infarction, previous vitamin K antagonist (VKA) use, and most frequent concomitant medications; abbreviations as in Figure 2.

The randomized controlled trials comparing warfarin with novel anticoagulants such as DE (11) provide a unique opportunity to compare potential differential effects on the decline in renal function associated with VKAs and the novel thrombin antagonist DE. Consistent with previous observations reporting a decline in renal function with warfarin depending on the INR of therapeutic range (28), we found that DE treatment was associated with a smaller decline in renal function over time compared with warfarin. In agreement with previous studies (31), patients on warfarin exhibiting INR values mainly above the therapeutic range, or those who were VKA experienced, had a more prominent decline in GFR according to the estimation with CKD-EPI, the most precise predictor of renal function decline. The small differences between treatments in GFR declines early after entering the study were nominally significant but not robust after adjustment. The addition or dose adaptation of medications, such as amiodarone, diuretics, or renin angiotensin blockers, could have played a role or even direct hemodynamic or renal effects of DE, which have not been investigated. In addition, the more proximal inhibition of hemostasis by VKAs involves factor VII antagonism, with potential beneficial vascular effects, including plaque stabilization. The importance of this (if any) and the underlying mechanism are undetermined.

Interestingly, factor Xa and thrombin are associated with vascular inflammation involving the thrombin receptor PAR2 (32). In another model of inflammatory atherosclerosis, the thrombin inhibitors DE (8) and melagatran (9) reduced vascular inflammation, oxidative stress, and plaque load. Furthermore, increased calcifications induced by inhibition of the vitamin K-dependent protein matrix gamma-carboxyglutamic acid (Gla/MGP) by warfarin (3,4) might be involved in the calcification of renal arteries (2) and increase plaque load and plaque morphology (**Central Illustration**) (1,5). In agreement with this hypothesis, patients with diabetes in the present study had a more progressive decline in renal function with warfarin compared with DE. Furthermore, the decline in renal function was more pronounced in those patients with more vitamin K

CENTRAL ILLUSTRATION **Vascular Calcification, Arterial Damage, and Decline in Renal Function May Be Triggered by the Inhibition of the Vitamin K-Dependent Protein Matrix Gammacarboxyglutamic Acid (Gla/MGP) by Vitamin K Antagonists**



Böhm, M. et al. J Am Coll Cardiol. 2015; 65(23):2481–93.

Matrix Gla protein (MGP) inhibits the osteoinductive function of bone morphogenetic protein (BMP). This function of MGP depends on gamma-carboxyglutamatic acid residues, which are modified in a vitamin K–dependent manner. In addition to blocking gamma-carboxylation of coagulation factors, warfarin inhibits this function of MGP, which in turn, antagonizes the inhibitory role of MGP in the process of vascular calcification, resulting in arterial damage and a decline in renal function.

depletion under warfarin, demonstrated by an increased INR out of the therapeutic range. This finding was associated in previous studies with a progressive decline in renal dysfunction (31), adding plausibility to the hypothesis that the decline in renal function is associated with VKA treatment. Mechanistically, biopsy-proven episodic glomerular hemorrhage could play a role. Although renal function seems to be differentially affected by DE and warfarin, the efficacy and safety of DE (33), as well as other novel anticoagulants (34), in preventing stroke were better or similar compared with warfarin. Furthermore, previous impaired renal function is associated with reoccurrence of AF (35). Thus, changing the quality of AF by renal function also could have had an effect on outcomes.

STUDY LIMITATIONS. The treatment duration of patients varied between 12 and 37 months, and thus the comparisons at 24 and 30 months were based on a subset of patients. The statistical model used in our analysis accounts for these "structural" dropouts, and the large study population ensures sufficient statistical power for reliable comparisons. The mean treatment duration of ~24 months was short compared with the need for life-long anticoagulant treatment to prevent thromboembolic events. Therefore, the decline in renal function might be underestimated in the present analysis compared with long-term treatment in general practice. The assumption of a deleterious effect of vitamin K depletion over time is supported by the group of patients with previous VKA treatment who had a more pronounced decline in estimated GFR with warfarin compared with VKA-naive patients. Validation of these results in a future study is warranted to confirm the deleterious effects of VKA treatment on renal function.

CONCLUSIONS

In elderly patients with AF, there was a decline in renal function that, at 30 months of follow-up, was greater in patients treated with warfarin compared with DE-treated patients and most pronounced in patients with previous treatment with VKAs or in patients with diabetes. The decline in renal function with both treatments indicates the need for monitoring of renal function at regular intervals (e.g., once a year or more frequently in certain clinical situations when it is suspected that the renal function could deteriorate) during oral anticoagulation treatment with warfarin as well as with DE. The more rapid reduction in renal function during warfarin treatment may be relevant in the selection of anticoagulants for long-term treatment. Prospective validation of these results in future trials is warranted.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In patients with nonvalvular AF, renal function declined less during treatment with DE, 110 or 150 mg twice daily, than in those randomized to receive warfarin. This outcome may be due to inhibition by warfarin of vitamin K–dependent matrix gamma-carboxyglutamic acid (Gla/MPG).

TRANSLATIONAL OUTLOOK: Prospective trials are needed to confirm a potential advantage of target-specific oral anticoagulants over warfarin with respect to renal dysfunction during long-term treatment and to establish the mechanism by which this accrues.

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APPENDIX For a supplemental table and figure, please see the online version of this article.

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