

# Investigation on Dabigatran Etextilate and Worsening of Renal Function in Patients with Atrial fibrillation: The IDEA Study

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## **Abstract**

**Background and Objectives** Warfarin-related nephropathy is an unexplained acute kidney injury, and may occur in patients with supratherapeutic INR, in the absence of overt bleeding. Similar findings have been observed in rats treated with dabigatran etexilate. We conducted a prospective study in dabigatran etexilate-treated patients to assess the incidence of dabigatran-related nephropathy and to investigate the possible correlation between dabigatran plasma concentration (DPC) and worsening renal function.

**Method** One hundred and seven patients treated long term with dabigatran etexilate for non-valvular atrial fibrillation (NVAF) were followed up for 90 days. DPC, serum creatinine (SCr) and serum cystatin C were prospectively measured. Ninety five patients had complete follow-up data and were evaluable for primary endpoint.

**Results** Eleven patients had supratherapeutic DPC, defined as DPC higher than 200 ng/ml at study enrolment, but at the end of follow-up no patient showed a persistent increase in SCr. No patients experienced acute kidney injury.

**Conclusions** Our study shows that no persistent renal detrimental effect is associated with dabigatran treatment. An increase in SCr during dabigatran treatment is reversible and it seems to be unrelated to dabigatran itself.

## **Introduction**

Anticoagulant therapy with vitamin K antagonists (VKAs) and, more recently, with direct oral anticoagulants (DOACs) is the mainstay of stroke prevention in non-valvular atrial fibrillation (NVAF) [1]. Despite being highly effective with a stroke rate reduction of nearly 62% compared with placebo [2], anticoagulant agents are associated with major bleeding that can eventually be lethal [3]. Non-haemorrhagic adverse events with anticoagulation may also occur, although quite rarely [4–8].

Recently, a new complication of VKAs has been described, i.e. warfarin-related nephropathy (WRN), also

known as warfarin-related renal impairment. It consists of an unexplained acute kidney injury, defined as a serum creatinine (SCr) increase greater than 0.3 mg/dl within 1 week of a supratherapeutic INR (international normalised ratio), without overt bleeding [9–14]. WRN seems to reduce 1-year survival and to accelerate renal dysfunction, especially but not only in patients with pre-existing chronic kidney disease (CKD) [10, 12, 13]. As it has been proposed that WRN could be due to glomerular micro-bleeds [15, 16], the same complication could also occur with DOACs. Indeed, similar findings have been observed in rats treated with dabigatran etexilate [17]. Alternatively, more recently, renal tubule occlusion by red blood cells has been suggested as a possible pathogenic mechanism [18].

Based on such evidence, we conducted a prospective study in patients treated with dabigatran for NVAF to assess the incidence of anticoagulant-related nephropathy and to investigate whether dabigatran plasma concentration (DPC) was related to the worsening of renal function.

## **Patients and Methods**

### **Study Overview**

This was an observational prospective single-centre study. Our local Ethics Committee approved the study. All patients provided written informed consent. The primary analyses of the data were performed in the Laboratory of Medical Statistics, at the Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy.

### **Study Design**

Patients on treatment with dabigatran etexilate with NVAF were prospectively followed at four time-points: T0

(enrolment time), T1 (7 days after enrolment), T2 and T3 (60 and 90 days after enrolment, respectively). Time-point spacing was based on previous studies focusing on WRN. It is known that patients developing WRN show a peak in SCr during the first week, then SCr remains elevated for about 3 months, slowly recovering but never returning to baseline levels. Blood samples were harvested to determine DPC, measured as diluted thrombin time (dTT, HEMOCLOT ®) [19, 20], at T0 and T1; SCr and serum cystatin C (CysC) were measured at all four time points. Figure 1 summarizes the study design: TSTART is the time point when dabigatran etexilate therapy was started and refers to SCr available at that moment.

### **Study Outcomes**

The primary objective of this study was to estimate the incidence of (unexplained) renal injury at 90 days in patients with a DPC higher than the therapeutic range at enrolment. DPC, measured as dTT, was defined as supra-therapeutic, if higher than 200 ng/ml. This is in accordance with the practical guide on management of DOACs [21] proposed by the European Heart Rhythm Association (EHRA). Unexplained acute renal injury was defined, according to the WRN definition, as an increase in SCr of greater than 0.3 mg/dl from enrolment to 90 days, without clinical evidence of haemorrhage.

The secondary objective of this study was to evaluate the incidence of renal damage at each time point during follow-up and to assess the persistence or regression of kidney function impairment at the different time points of the study.

### **Study Population**

All the patients followed for NVAF at ASST Vimercate, Department of Internal Medicine, (Vimercate, MB, Italy) were assessed for eligibility. Inclusion criteria were age > 18 years, confirmation of non-valvular cardiomyopathy [22] by colour Doppler echocardiography, ongoing treatment with dabigatran etexilate, and ability to sign the informed consent form. Patients were excluded in case of inability to follow the study protocol, altered thyroid function during the last 6 months, severe renal failure (< 30 ml/min), and concomitant corticosteroid therapy. The following information was collected at baseline (T0): age, sex, body mass index (BMI), and dabigatran etexilate dosage (e.g. 110 mg twice daily (BID) or 150 mg BID), and

dabigatran etexilate therapy duration. CHA2DS2-VASc [23] and HAS-BLED scores [24] were calculated for each patient. A relevant medical history was collected, and concurrent medications were recorded.

Follow-up was planned 1 week after enrolment (T1), at 2 months (T2) and at 3 months (T3): relevant medical information, such as hospitalizations, cardiovascular events and variation in concomitant medications were recorded.

### **Sample Material and Laboratory Methods**

At all time-points, blood samples were collected to determine SCr and CysC. Furthermore, at study enrolment and 1 week later (respectively, T0 and T1) blood samples were collected to determine DPC. Blood samples were harvested at trough concentration of dabigatran (e.g. just before dabigatran etexilate intake), via a standard procedure (cubital/cephalic vein puncture with butterfly/Vacutainer®), and then immediately centrifuged (3500 rpm for 12 min, at room temperature). The tubes were then stored at  $-80^{\circ}\text{C}$  until analysis. DPC measured as dTT and expressed as ng/ml was determined on defrosted platelet-free plasma, derived from citrated blood samples, with the HEMOCLOT® assay [19,20], on a BCS-XP analyser (Siemens Healthcare Diagnostics, Marburg, Germany). SCr and CysC samples were collected in serum-separating tubes and were submitted to the same centrifugation and storage process. Serum concentration was measured by Roche-Hitachi Cobas 6000, Analytical system.

### **Statistical Analysis**

Demographic and clinical characteristics of patients were summarized by absolute numbers and percentages for categorical variables and by median, first and third quartiles for quantitative variables. For descriptive purposes, the variable distribution was reported firstly within two groups of subjects according to the dabigatran etexilate dosage (110 mg BID or 150 mg BID) and secondly within two groups of subjects according to DPC at T0 ( $< 200$  ng/ml,  $\geq 200$  ng/ml). The variable distribution between the two groups of patients mentioned above was compared using Fisher's exact test for categorical variables and the non-parametric Wilcoxon rank sum tests for continuous variables.

To evaluate the relationship between DPC at T0 (response) and age (explanatory variable) a linear regression model was fitted.

To evaluate the incidence of renal damage at T3 (primary endpoint) the inference was based on

95% confidence intervals (CIs). Fisher's exact method was applied [25].

To evaluate renal damage at each time-point during the follow-up (secondary endpoint) the proportion of renal damage was computed with the pertinent 95% CI obtained with exact method. The incidence of renal damage, according to age, sex, BMI and daily dabigatran etexilate dosage assumption, was estimated by a generalized linear regression model with binomial error on all patients with complete information on the occurrence of renal damage from T0 to T3.

Furthermore, evaluation of the persistence or regression of renal impairment during 90 days of follow-up was performed through a mixed-model regression analysis [26] on all patients with complete information from T0 to T3. At the beginning of the study, it was not possible to compute sample size because no information was available on the expected number of renal injuries in patients with supra-therapeutic DPC. For practical considerations, the study was based on a 1-year recruitment (about 100 patients expected).

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## **Results**

From 1 July to 23 October 2015 we recruited 107 patients on dabigatran etexilate for NVAf. Sixty-one patients (57% of the overall study population) were receiving dabigatran etexilate 110 mg BID and the remaining 43% dabigatran etexilate 150 mg BID. The median age was 79 years and the median CHA<sub>2</sub>DS<sub>2</sub>-VASc score was five, while the median HAS-BLED score was three.

Patient characteristics are described in Table 1, according to dabigatran etexilate dosage. The patients treated with 110 mg BID were older than those treated with 150 mg BID (median age 83 years vs. 73 years,  $p < 0.001$ ) and were more frequently women (59% vs. 37%,  $p = 0.032$ ).

Patients treated with the two dosages had a similar DPC, both at T0 and T1:

median DPC at T0 was 106.3 ng/ml in the dabigatran etexilate 110 mg group and 99 ng/ml in dabigatran etexilate 150 mg ( $p = 0.389$ ) and median DPC at T1 was 128.9 ng/ml in dabigatran etexilate 110 mg group versus 99.2 ng/ml in dabigatran etexilate 150 mg group ( $p$

= 0.072).

Table 2 shows the demographic and clinical characteristics for patients with therapeutic DPC and suprathereapeutic DPC. We observed that CHA2DS2-VASc distributions were significantly different according to DPC at T0 ( $p = 0.015$ ).

The median CHA2DS2-VASc in patients with therapeutic DPC was four, whereas the median CHA2DS2-VASc in patients with suprathereapeutic DPC was five. When considering SCr at Tstart, no statistically significant difference was observed between patients with low-normal DPC ( $< 200$  ng/ml), and patients with higher DPC: median SCr was 0.92 mg/dl in patients with therapeutic DPC and 0.98 mg/dl in patients with suprathereapeutic DPC at T0 ( $p = 0.486$ ).

With regard to age distribution according to DPC at T0, median age was higher in patients with supra-therapeutic DPC, even though the difference was not statistically significant. Moreover, when DPC was considered as a continuous variable, a statistically significant association between age and DPC was obtained: increasing age was associated with increasing DPC, as evaluated by linear regression model results. At T0, mean DPC increased by 2.672 ng/ml (95% CI 1.007–4.337) each year of increase in age.

Table 3 describes concomitant drug usage in the study population and according to DPC at T0. No influence of the different concomitant drugs was observed on DPC.

Due to technical reasons (e.g. tube breakage during defrosting procedures), DPC data were missing in two patients at T0. From T0 to T1 one patient, from T1 to T2 five patients and from T2 to T3 four patients were lost to follow-up. For these ten patients the exact withdrawn time was unknown. Of the remaining 95 patients with complete follow-up information, 11 had supra-therapeutic DPC at T0. Thus, the primary endpoint was assessed on 11 patients. In this subset, the incidence of renal injury at T3 was zero (95% CI 0–0.285). On the other hand, in the 84 patients with therapeutic DPC, only two patients showed a SCr increase higher than 0.3 mg/dl at T3 for a total incidence of 0.024 (95% CI 0.003–0.083). There was no statistically significant difference in renal injury at the end of follow-up between patients with therapeutic or supra-therapeutic DPC at T0. The difference in incidence values was 0.024 (95% CI – 0.234 to 0.083). No patients needed a dabigatran dosage modification according to renal function. No dosage was modified throughout the study according suprathereapeutic

concentration of the drug. Furthermore, no patients experienced acute kidney injury.

If we consider all time points, 15 patients had suprathreshold DPT at T0; one patient was lost to follow-up just after T0. From T0 to T1, the information was available for 14 patients, and among these, a SCr increase was present in one patient (proportion of renal damage: 0.714, 95% CI 0.002–0.339). From T1 to T2, the information was available of renal damage: 0.167, 95% CI 0.0209–0.484). From T2 to T3, the information was available in 11 patients and one of them had renal damage (proportion of renal damage: 0.091, 95% CI 0.002–0.413). If we consider all time points, 90 patients had therapeutic DPC at T0. Renal damage was observed in six out of 90 patients, from T0 to T1 (proportion of renal damage: 0.067, 95% CI 0.025–0.139). SCr increase occurred in four patients out of 87 from T1 to T2 (proportion of renal damage: 0.046, 95% CI 0.013–0.114), and in five patients out of 84 from T2 to T3 (proportion of renal damage: 0.060, 95% CI 0.020–0.133).

Due to the small number of patients and renal injuries, we could not perform a multivariate analysis to correlate renal injury with the different variables. We therefore performed univariate analysis and found that no covariates (age, sex, BMI and dabigatran etexilate dosage) were significantly associated with renal damage. To evaluate the persistence of renal damage, in the entire sample of 95 patients with complete follow-up information, we observed that among the patients who developed SCr damage at T1, 59.4% (95% CI 8–100,  $p = 0.353$ ) of them showed persistence of SCr damage at T2 too. No patients, however, showed persistence of SCr damage at T3. Therefore, we can affirm that in our study population, the SCr increase observed in dabigatran etexilate-treated patients was reversible in all cases.

## **Discussion**

In recent years, WRN has been described [9, 10]. Although it is more frequent in patients with CKD, recent studies suggest that it can also occur in any VKA-experienced patients, and it is associated with age, diabetes mellitus, hypertension and cardiovascular disease [10]. Evidence suggests that WRN may influence mortality, and is associated with progressive loss of renal function [11–13]. Regardless of warfarin use, a renal injury could theoretically occur in any patient treated with anticoagulant therapy and no prospective data are available on DOACs. A few case reports have been published describing a possible kidney injury related to dabigatran



etexilate [17, 18] and apixaban [27]. The present study is the first observational prospective investigating a relationship between DPC and renal injury, in patients affected by AF and treated with dabigatran etexilate. Retrospective analysis by Böhm, pertaining to RE-LY trial [28], shows that compared to warfarin-treated patients, dabigatran etexilate treatment was associated with a lower incidence of renal function decline. Renal impairment was amplified in diabetic patients and in experienced VKA users. The same study showed that patients who were in the therapeutic range for a short time exhibited the most rapid decline in GFR [29]. In a Taiwanese nationwide retrospective cohort study in Asian patients with NVAF, dabigatran etexilate was associated with a lower risk of acute kidney injury compared to warfarin, for patients with CKD and those without CKD [30]. Furthermore, a retrospective study on 9769 patients with NVAF showed that dabigatran etexilate, rivaroxaban and apixaban were associated with a reduced risk of  $\geq 30\%$  decline in eGFR, and doubling of SCr and AKI compared with warfarin [31].

In the 107 patients we enrolled, 57% were treated with dabigatran etexilate 110 BID and, as expected, they were older than those treated with the highest dose. There was no difference in Tstart renal function between dabigatran etexilate 110 mg and dabigatran etexilate 150 mg subjects, and those treated with either of the two doses had comparable DPCs but there was a non-significant trend to a higher DPC in patients taking the lower dosage. Linear regression analysis showed that DPC increases by a factor of 2.6–3.3 ng/ml with each increase in year of age. This is likely due to a progressive impairment of drug metabolism, in association to patient ageing. Eikelboom et al. in a pre-specified subanalysis of the RE-LY trial showed that there is a significant treatment-by-age interaction. The interaction with age is evident for extracranial bleeding, but not for ICH, with the risk of the latter being consistently reduced with both dosages of dabigatran etexilate, compared with warfarin, irrespective of age [32]. Our findings confirm Owada's results showing a high DPC in high-risk patients (fragile patients with a high CHA2DS2- VASc score) [33].

The primary outcome of our study was the incidence of renal injury at 3 months in patients with T0 supratherapeutic DPC (per EHRA definition) [21]. In the 11 patients with the highest DPC at T0 (e.g. DPC  $\geq 200$  ng/ml), no patient showed a SCr increase higher than 0.3 mg/dl at 3 months. As a secondary outcome, we considered all patients with therapeutic or supratherapeutic DPCs and we observed persistence of renal damage at different timepoints. Among the seven patients who developed renal damage between T0 and T1, 59.4% showed persistence of

SCr damage at T2 and none of them showed persistence of renal injury at T3.

Therefore, it appears that in our study population, the SCr increase observed in dabigatran etexilate-treated patients was reversible in all cases. These data, so far, do not completely clarify whether a variation in DPC induces renal injury or vice versa. Nevertheless, as far as the results of the present study are concerned, we can state that a high DPC itself does not seem to induce an SCr increase. After renal excretion, DPC is higher in patients with a higher SCr and CysC. Dabigatran etexilate does not have a deleterious effect on renal function but renal function itself influences DPC. Patients with different DPCs (e.g. suprathreshold vs. therapeutic DPC, regardless of the definition) had similar median SCr levels, and displayed a similar rate of SCr increase.

This study has several limitations, which are worth considering. First, our results are derived from a relatively small number of patients, and therefore the results cannot be extrapolated to another population. Furthermore, although this study was designed to identify patients with high DPC at trough during dabigatran etexilate treatment, the small sample size does not yet allow us to suggest a possible DPC cut-off for identifying patients with a higher risk of renal injury during DE treatment. Assuming an incidence of warfarin-related nephropathy of 10% in patients with no CKD, we would have expected at least one or two occurrences of dabigatran-related nephropathy. Since we found an incidence of 11.6% of patients with supra-therapeutic DPC in our population, we would probably need at least twice or three times as many patients to properly investigate this. Most recruited patients were prescribed dabigatran etexilate during hospitalization, mainly because of acute heart failure. This explains the high-risk profile, and could explain the initial renal impairment, which later, over time, improved and stabilized. For this reason, our sample reflects a high-risk population that would infrequently be enrolled in major phase III trials. Though dosage choices were made according to international recommendations [21] and to the Summary of Product Characteristics [34], we cannot exclude a physician influence on dosage prescription. We did not set any exclusion criteria on previous dabigatran etexilate therapy duration, but we did not find any influence on DPC per dabigatran etexilate treatment duration. The time point allocations can be questioned, but we decided to repeat DPC, SCr, CysC and eGFR after 1 week because in WRN kidney damage peaks 1 week after suprathreshold INR measurement. Furthermore, we decided to repeat the measurement of renal function 3 months later, because WRN persists to 90 days and we wanted to observe

whether a high DPC had long-lasting consequences for kidney function. We arbitrarily set a second time point at 2 months. We deliberately did not perform urinalysis. WRN is defined by an increase in SCr and not by haematuria; indeed haematuria is an exclusion criterion. Monitoring of microscopic haematuria could have been an exploratory endpoint, but we decided to focus on an SCr increase and kidney function. Lastly, although WRN can occur also in patients with normal renal function, it is more frequently encountered in patients with CKD. Our population had a median SCr of 0.93 mg/dl and a median eGFR of 63.01 ml/min. A larger population study could help to define whether patients with moderate CKD would have a higher risk of renal function impairment as a result of dabigatran etexilate treatment. Patients with severe CKD cannot be treated with dabigatran [34]. Aside from the several limitations, this is the first study specifically designed to evaluate the presence and the incidence of a dabigatran-related renal impairment in humans. It is a prospective study and is the first study to evaluate renal impairment through more sensible and specific methods such as CysC and the 2012 CKD-EPI cystatin C-creatinine formula.

## **Conclusion**

In conclusion, our study does not show any persistent detrimental effect of dabigatran etexilate itself on renal function. We did not find any connection between high DPC and renal injury. SCr increases during dabigatran etexilate treatment are reversible and are probably not related to the drug itself. However, since the renal events were few and all were reversible, this study does not provide much in answering how many patients would be needed in a future study to definitively exclude or confirm the existence of dabigatran-related nephropathy.

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**Table 1** Baseline characteristics of the patients. For quantitative variables the median values (first quartile, third quartile) are reported

Patient characteristics	Total	DE110	DE150	P value
Female sex (%)	49.53%	59.02	36.96	0.032
Age, y	79 (72.5–84)	83 (80–88)	73 (69–77.5)	< 0.001
BMI (kg/m <sup>2</sup> )	26.17 (23.23–28.42)	26.76 (23.81–28.66)	25.71 (22.04–28.30)	0.213
CHA2DS2-VASc score	5 (3.5–5)	5 (4–6)	4 (3–5)	0.001
HAS-BLED score	3 (2–3)	3 (2–3)	2 (2–3)	0.119
Serum creatinine at T0	0.93 (0.78–1.06)	0.96 (0.76–1.08)	0.88 (0.79–1.00)	0.323
eGFR at T ml/min	63.01 (49.56–76.05)	56.40 (41.25–69.55)	67.75 (57.57–77.74)	0.002
DPC at T0 ng/ml	102.9 (70.2–164.6)	106.30 (71.25–171.85)	99.00 (63.15–149.97)	0.389
DPC at T1, ng/ml	115.65 (80.12–166.97)	128.90 (82.25–175.05)	99.2 (76.0–124.70)	0.072

**Table 2** Baseline characteristics of patients, according to DPC at T0

Patient characteristics	DPC < 200, ng/ml	DPC ≥ 200, ng/ml	P value
Female sex (%)	42 (46.67%)	10 (66.67%)	0.174
Age, year	80 (74–86)	84 (81–87)	0.136
BMI, kg/m <sup>2</sup>	26.2 (23.29–28.65)	25.84 (21.37–27.84)	0.558
CHA2DS2-VASc score	4 (4.00–5.75)	5 (5–6)	0.015
HAS-BLED score	3 (2–3)	2 (2–3)	0.250
Serum creatinine at TSTART, mg/dl,	0.92 (0.77–1.04)	0.98 (0.83–1.02)	0.486
Serum creatinine at T0, mg/dl	0.90 (0.76–1.02)	1.00 (0.82–1.29)	0.053
eGFR at T0, ml/min	65.98 (53.56–77.58)	47.23 (36.49–61.53)	0.001



**Table 3** Number and percentage of patients taking concomitant drugs

<b>Concomitant drugs</b>	<b>Total</b>	<b>DPC &lt; 200, ng/ml</b>	<b>DPC ≥ 200, ng/ml</b>	<b>P value</b>
<b>ACE-inhibitors</b>	37 (34.58%)	29 (32.22%)	8 (53.33%)	0.146
<b>ARBs</b>	40 (37.38%)	36 (40%)	3 (20%)	0.161
<b>Diuretics</b>	62 (57.94%)	48 (53.33%)	12 (80%)	0.089
<b>Beta-blockers</b>	72 (67.29%)	58 (64.44%)	13 (86.67%)	0.135
<b>Proton pump inhibitors</b>	51 (47.66%)	45 (50%)	5 (33.33%)	0.274
<b>Verapamil</b>	1 (0.93%)	1 (1.11%)	0 (0%)	1.000
<b>Other calcium-antagonists</b>	26 (24.3%)	23 (25.56%)	3 (20%)	0.757
<b>Amiodarone</b>	7 (6.54%)	7 (7.78%)	0 (0%)	0.590
<b>Digoxin</b>	13 (12.15%)	11 (12.22%)	2 (13.33%)	1.000
<b>ASA</b>	2 (1.87%)	0 (0%)	1 (6.67%)	0.143

**Figure 1**

Study design: analytes dosed at each time point.  $T_{START}$  time point before starting therapy with dabigatran etexilate,  $T_0$  time point 0—study enrolment,  $T_1$  time point 1—1 week after enrolment,  $T_2$  time point 2—2 months after enrolment,  $T_3$  time point 3—3 months after enrolment,  $SCr$  serum creatinine,  $DPC$  dabigatran plasma concentration,  $CysC$  serum cystatin C

