Dabigatran etexilate for secondary stroke prevention: the first year experience from a multicenter short-term registry

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Abstract

Background: There are growing concerns for the side effects of dabigatran etexilate (dabigatran), including higher incidence of dyspepsia and gastrointestinal bleeding. We conducted a multicenter early implementation study to prospectively evaluate the safety, efficacy and adherence to dabigatran for secondary stroke prevention.

Methods: Consecutive atrial fibrillation (AF) patients with ischemic stroke (IS) or transient ischemic attack (TIA) received dabigatran for secondary stroke prevention during their hospital stay according to American Heart Association recommendations at five tertiary care stroke centers. The study population was prospectively followed and outcomes were documented. The primary and secondary safety outcomes were major hemorrhage and all other bleeding events respectively defined according to RE-LY trial methodology.

Results: A total of 78 AF patients (mean age 71 ± 9 years; 54% men; 81% IS, 19% TIA; median CHADS₂ [Congestive heart failure, Hypertension, diabetes mellitus, age >75 years, prior stroke or TIA]; range 2–5) score 4 were treated with dabigatran [(110mg bid (74%); 150mg bid (26%))]. During a mean follow-up period of 7 ± 5 months (range 1–18) we documented no cases of IS, TIA, intracranial hemorrhage, systemic embolism or myocardial infarction in AF patients treated with dabigatran. There were two (2.6%) major bleeding events (lower gastrointestinal bleeding) and two (2.6%) minor bleedings [hematuria ($n = 1$) and rectal bleeding ($n = 1$)]. Dabigatran was discontinued in 26% of the study population with high cost being the most common reason for discontinuation (50%).

Discussion: Our pilot data indicate that dabigatran appears to be safe for secondary stroke prevention during the first year of implementation of this therapy. However, high cost may limit the long-term treatment of AF patients with dabigatran, leading to early discontinuation.

Keywords: atrial fibrillation, dabigatran etexilate, secondary prevention, stroke, transient ischemic attack

Introduction

Dabigatran etexilate (dabigatran) is a novel oral thrombin inhibitor approved for the risk reduction of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (AF) [Weimar *et al.* 2012]. The approval of this new oral anticoagulant (NOAC) was based on the large phase III clinical trial of stroke prevention in AF, the

RE-LY (Randomized Evaluation of Long-Term Anticoagulant therapy) study [Connolly *et al.* 2009; Diener *et al.* 2010].

However, concerns regarding the side effects of dabigatran remain, including higher incidence of dyspepsia and gastrointestinal bleeding – especially in older patients and those with low body weight

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[Legrand *et al.* 2011; Bene *et al.* 2012]. Moreover, there was a trend towards a higher incidence of myocardial infarction (MI) in patients treated with dabigatran in the RE-LY study [Connolly *et al.* 2009; Diener *et al.* 2010]. Experts worldwide recommend caution with the use of dabigatran in clinical practice given a number of unresolved issues including lack of effective laboratory monitoring, lack of antidote as well as safety concerns about use in elderly and in patients with renal insufficiency [Stollberger and Finsterer, 2012a].

The aim of the present multicenter study was to prospectively evaluate the safety, efficacy and adherence to dabigatran for secondary stroke prevention in an 'everyday clinical practice' setting.

Methods

Consecutive AF patients with ischemic stroke (IS) or transient ischemic attack (TIA) were treated with dabigatran for secondary stroke prevention according to American Heart Association (AHA) recommendations [Wann *et al.* 2011] at five tertiary care stroke centers (Department of Neurology, Attikon Hospital, Athens, Greece; Department of Neurology, Alexandroupolis, Greece; Department of Neurology, Singapore, Singapore; Department of Neurology, Bochum, Germany; and Comprehensive Stroke Research Center, Birmingham, Alabama, USA) during a 2-year study period (May 2011 to May 2013). Dabigatran was initiated early after ischemic symptom onset and during patients' hospital stay.

All patients were included in a computerized database. Their demographic characteristics, vascular risk factors and secondary prevention therapies during hospitalization and after discharge were documented as previously described in similar studies by our international collaborative group [Tsigoulis *et al.* 2010, 2011, 2012; Zhao *et al.* 2011]. Stroke risk stratification was performed in AF patients using the CHADS₂ (congestive heart failure, hypertension, diabetes mellitus, age >75 years, prior stroke or TIA) score [Gage *et al.* 2004]. AF patients were prospectively followed up at outpatient stroke clinics of our respective institutions and were clinically re-evaluated at regular 3-month intervals during the follow-up period by an attending neurologist as previously described [Tsigoulis *et al.* 2010]. During the follow-up period outcomes (IS, TIA, systemic embolism, pulmonary embolism, MI) were documented according to RE-LY methodology [Ezekowitz *et al.* 2009]. The

primary safety outcome was major hemorrhage, defined according to RE-LY criteria as a reduction in the hemoglobin level of at least 20 g per liter, transfusion of at least 2 units of blood, or symptomatic bleeding in a critical area or organ [Connolly *et al.* 2009]. Secondary safety outcomes included all other bleeding events other than major hemorrhage and were subsequently classified as minor bleedings.

Statistical analyses

Continuous parametric and nonparametric data are presented as mean $\pm$ standard deviation (SD) or as median (range) respectively. Noncontinuous variables are presented as percentages. The Statistical Package for Social Science (SPSS Inc., version 13.0 for Windows) was used for statistical analyses.

Results

We prospectively enrolled 78 AF patients (63 with IS and 15 with TIA) with a mean age of 71 ± 9 years (54% men, 46% women). The median CHADS₂-score was 4 (range 2–5). Approximately a quarter of patients were treated with dabigatran dose of 150 mg twice daily (bid) (26%), while the remaining AF patients ($n = 58$; 74%) received a dabigatran dose of 110 mg bid. Baseline characteristics and stroke risk factors are shown in Table 1.

The study population was prospectively followed for a mean follow-up period of 7 ± 5 months (range 1–18). The outcome events of interest during the follow-up period are presented in Table 2. There were no cases of IS, TIA, systemic embolism or myocardial infarction. There were two major adverse events (2.6%) with two patients presenting with major lower gastrointestinal hemorrhage. Both patients with major lower gastrointestinal hemorrhage required hospitalization and multiple transfusions to be stabilized. Dabigatran was discontinued and, after 1 month, patients received oral anticoagulation with coumadin. We documented two minor adverse events (2.6%) in another two patients (one case of rectal bleeding and one case of hematuria). Creatinine clearance was >50 ml/min/1.73 m² in the four patients who presented with minor or major bleeding events. Two out of the four patients with adverse events (one major and one minor bleeding) were treated with dabigatran 150 mg bid, while the remaining two (one major and one minor bleeding) received

Table 1. Baseline characteristics of the study population ($n = 78$).

Characteristic	
Mean age, years (SD)	71 (9)
Male gender, %	54%
Acute ischemic stroke	81%
Transient ischemic attack	19%
Paroxysmal atrial fibrillation	23%
Median CHADS ₂ score (range)	4 (2–5)
Median NIHSS-score (range)	5 (0–14)
Gastroprotective agents (%)	54%
Dabigatran 110 mg bid (%)	74%
Dabigatran 150 mg bid (%)	26%

bid, twice daily; CHADS₂, congestive heart failure, hypertension, diabetes mellitus, age >75 years, prior stroke or transient ischemic attack; NIHSS, National Institutes of Health stroke scale.

Table 2. Safety and efficacy outcomes of dabigatran during the follow-up period.

Outcomes	
<i>Efficacy outcomes</i>	
Ischemic stroke	0%
Transient ischemic attack	0%
Systemic embolism	0%
Myocardial infarction	0%
<i>Safety outcomes</i>	
Intracranial hemorrhage	0%
Major bleed	2.6% ($n = 2$)*
Minor bleed	2.6% ($n = 2$) [§]

*Two cases of lower gastrointestinal bleeding.
[§]One case of hematuria and one case of rectal bleeding.

110 mg of dabigatran bid. No events of intracranial bleeding were reported.

In our study cohort, treatment with dabigatran was terminated in 20 patients (26%); in half of these patients this decision was made due to the high treatment cost. Other reasons for dabigatran discontinuation were the aforementioned side effects in three patients (15%) and patient's non-compliance in another three cases (15%). Dyspepsia, bloating and flatulence were the side effects reported in two out of three patients who discontinued dabigatran. Finally, dabigatran was substituted with coumadin in four patients (20%) by primary care physicians, without any of these patients experiencing any side effects and without

any reason provided by the primary care physician (Table 3). Finally, in two patients who discontinued dabigatran (10% of cases with dabigatran discontinuation) an embolic event (one case of IS and one case of systemic embolism) occurred when coumadin was substituted for dabigatran.

Discussion

Our pilot data indicate that dabigatran appears to be safe for secondary stroke prevention during the first year of implementation of this therapy during hospitalization for acute cerebral ischemia. However, high cost may lead to early discontinuation and therefore limit the long-term treatment of AF patients with dabigatran. Notably, all bleeding adverse events (both minor and major) affected the gastrointestinal system, while we documented no cases of recurrent stroke or intracranial bleeding in AF patients treated with dabigatran.

Comparing the baseline characteristics of our patients with those from a RE-LY trial subgroup including patients with a history of IS or TIA [Diener *et al.* 2010], we observed almost the same mean age (71 *versus* 70 years old) and a similar mean CHADS₂ score (4 in our study *versus* 3 or more in 89.6% of the RE-LY subgroup). However, our study represented fewer men (54% *versus* 64%) and more patients received a lower dabigatran dose (110 mg) in our cohort (74% *versus* 50%). Another notable difference is that our study was not randomized unlike RE-LY.

Only one case of pulmonary embolism, two cases of major hemorrhages and two cases of minor bleeding were reported during the follow-up period in our study. The annual rates of major bleeding were lower in our cohort (2.6%) compared with the RE-LY secondary prevention subgroup (2.7% for 110 mg bid dose and 4.2% for 150 mg bid dose) [Diener *et al.* 2010]. These findings are in line with a recently published population-based cohort study from Denmark [Larsen *et al.* 2013]. More specifically, stroke and systemic embolism incidences were not significantly different between dabigatran- and warfarin-treated patients, while patients treated with 110 mg dabigatran – similarly to RE-LY – had lower gastrointestinal bleeding rates compared with warfarin treated patients. The rates of overall mortality, intracranial bleeding, pulmonary embolism and MI – contrary to RE-LY – were

Table 3. Causes of dabigatran discontinuation.

Discontinuation of dabigatran	
Cost (n, %)	10 (50%)
Side effects	3 (15%)
Noncompliance	3 (15%)
Substitution by coumadin by primary care physician without the patient experiencing any side effects	4 (20%)
Total	20 (26% of patients initially treated with dabigatran)

lower in our dabigatran treated patients. Markedly, the major bleeding event rates (2.2% for 150 mg bid dose and 2.8% for 110 mg bid dose) were very close to our reported rate of major bleeding events (2.6%). The recently reported observations from the US Food and Drug Administration sponsored Mini-Sentinel distributed database provide further reassurance that bleeding rates associated with dabigatran are not higher than warfarin [Southworth *et al.* 2013]. Similarly, the use of dabigatran in the prevention of stroke and systemic embolism in patients with AF was found to be associated with an increase of 58% in the risk for gastrointestinal bleeding in a recent systematic review and meta-analysis [Holster *et al.* 2013].

Emerging case reports have indicated that older age [Legrand *et al.* 2011; Bene *et al.* 2012; Husari *et al.* 2013], lower [Legrand *et al.* 2011] or higher body weight [Wychowski and Kouides, 2012] and renal insufficiency [Legrand *et al.* 2011; Bene *et al.* 2012; Wychowski and Kouides, 2012] may increase the risk of bleeding in AF patients treated with dabigatran (Table 4). Age-related risk of bleeding with dabigatran is mainly associated with the concurrent renal impairment, although age alone can also be considered a separate risk factor due to the increased drug bioavailability and the concomitant bleeding complications [Stollberger and Finsterer, 2012b]. Patients with severe renal insufficiency [creatinine clearance (CrCl) < 30 ml/min/1.73 m²] were excluded by study design in the RE-LY trial, while patients with a CrCl = 30–49 ml/min/1.73 m² were also underrepresented (19% of the total study population). Similarly, only 0.02% of the patients had a bodyweight lower than 50 kg and only 0.17% weighted more than 100 kg in the RE-LY study population [Connolly *et al.* 2009; Jacobs and Stressman, 2011]. Therefore, clinicians should be cautious when administering dabigatran in these

specific AF patient subgroups. Of note though, none of the two patients with major bleeds events in our cohort were underweight or overweight nor did they present with impaired CrCl at the time of the bleeding event. Moreover, it should be kept in mind that there is a greater likelihood of reporting bleeding events in patients receiving dabigatran, due to the novelty of the treatment, than in ones receiving the time-tested warfarin [Southworth *et al.* 2013].

A retrospective review of the medical charts uncovered 44 bleeding episodes (27% of them major) in patients treated with dabigatran during the initial 2-month period after the release of the drug in Australia and New Zealand. Rectal bleeding was the most common bleeding complication in 19 of the aforementioned patients (44), while severe intracranial bleeding was reported in only one patient (0.02%). Four major factors were found to contribute to a bleeding episode: prescriber error (25%); moderate or severe renal impairment (58%); age over 80 years (67%); and bodyweight less than 60 kg (50%) [Harper *et al.* 2012]. We also documented lower gastrointestinal bleeding events as the most common bleeding complication in our cohort and our data, combined with the recent literature (Table 4), highlight the need for extra caution to uncover a potential history of rectal or colon or diverticulum bleeding prior to administering dabigatran in AF patients.

Interestingly, the main reason which was taken into account for dabigatran discontinuation in our cohort included high treatment cost and was not associated with either experienced side effects or patient's noncompliance. The high price of dabigatran may pose a serious barrier for not using it as a chronic treatment in patients with nonvalvular AF, leading to dabigatran substitution with much cheaper warfarin. However,

Table 4. Case reports of bleeding adverse events in patients receiving dabigatran during postmarketing surveillance.

Author	Age (years)	Gender	Weight (kg)	CrCl on admission (ml/min/1.73 m ²)	Dose (mg/twice daily)	Duration (months)	Adverse event	Outcome
Bene <i>et al.</i> [2012]	79	F	69	20,7	110	2	Rectal bleeding (major)	Favorable
Bene <i>et al.</i> [2012]	84	M	71	33,5	110	–	Rectal bleeding	Favorable
Husari <i>et al.</i> [2012]	85	M	–	85	110	6	Alveolar hemorrhage (major)	Favorable
Legrand <i>et al.</i> [2011]	84	F	40	32	75	4	Rectal bleeding (major)	Death
Legrand <i>et al.</i> [2011]	89	F	45	29	110	5	Epistaxis	Favorable
Wychowski and Kouides [2011]	66	F	123	15	150	2	Upper gastrointestinal bleeding (major)	Death

F, female; M, male.

according to the results from a cost-effectiveness study by Freeman and colleagues, dabigatran may be a cost-effective alternative to warfarin in patients over 65 years old with nonvalvular AF at high risk for stroke (CHADS₂ score >1 or equivalent). The cost-effectiveness largely depends on the pricing of both drugs and the pricing of coagulation tests for warfarin monitoring in each country [Freeman *et al.* 2011]. Thus, it is important for physicians to ensure that patients can afford dabigatran before prescribing it. For patients with AF who cannot afford dabigatran, warfarin will remain a relatively inexpensive and effective alternative [Alberts *et al.* 2012]. The lack of an antidote was another reason that prompted treating physicians to discontinue dabigatran in patients experiencing minor bleeding events. However, it should be noted that there are promising data from a phase I/II study indicating the feasibility of complete reversal of anticoagulant effects of dabigatran using a fragment of an antibody against dabigatran [Glund *et al.* 2013].

Certain limitations of the present study need to be acknowledged including the limited sample size and the short duration of the follow-up period. Moreover, there was no central adjudication of safety endpoints that were reported by local investigators. Finally, we have no control group with which to compare the rate of safety endpoints that were observed in the present cohort. It should be noted, however, that the aim

of the present multicenter study was to prospectively evaluate the safety, efficacy and adherence to dabigatran for secondary stroke prevention in an ‘everyday clinical practice’ setting, since there is limited postmarketing experience with this novel oral anticoagulant.

In conclusion, our pilot study provides reassurance regarding the safety of dabigatran for secondary stroke prevention, but caution against its early discontinuation due to the drug’s high cost. Clinicians should keep in mind that lower gastrointestinal bleeding events more commonly complicate dabigatran use when compared with intracranial hemorrhages, which constitute however the most feared and life-threatening complications. These findings underscore the importance of additional long-term data collection on the safety, efficacy and adherence to dabigatran given the fact that most AF patients with stroke require lifelong oral anticoagulation [Banerjee *et al.* 2011].

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Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

References

- Alberts, M., Bernstein, R., Naccarelli, G. and Garcia, D. (2012) Using dabigatran in patients with stroke: a practical guide for clinicians. *Stroke* 43: 271–279.
- Banerjee, A., Marin, F. and Lip, G. (2011) A new landscape for stroke prevention in atrial fibrillation: focus on new anticoagulants, antiarrhythmic drugs, and devices. *Stroke* 42: 3316–3322.
- Bene, J., Said, W., Rannou, M., Deheul, S., Coupe, P. and Gautier, S. (2012) rectal bleeding and hemostatic disorders induced by dabigatran etexilate in 2 elderly patients. *Ann Pharmacother* 46: e14.
- Connolly, S., Ezekowitz, M., Yusuf, S., Eikelboom, J., Oldgren, J., Parekh, A. *et al.* (2009) Dabigatran *versus* warfarin in patients with atrial fibrillation. *N Engl J Med* 361: 1139–1151.
- Diener, H., Connolly, S., Ezekowitz, M., Wallentin, L., Reilly, P., Yang, S. *et al.* (2010) Dabigatran compared with warfarin in patients with atrial fibrillation and previous transient ischaemic attack or stroke: a subgroup analysis of the RE-LY Trial. *Lancet Neurol* 9: 1157–1163.
- Ezekowitz, M., Connolly, S., Parekh, A., Reilly, P., Varrone, J., Wang, S. *et al.* (2009) Rationale and design of RE-LY: randomized evaluation of long-term anticoagulant therapy, warfarin, compared with dabigatran. *Am Heart J* 157: 805–810, 810 e801–802.
- Freeman, J., Zhu, R., Owens, D., Garber, A., Hutton, D., Go, A. *et al.* (2011) Cost-effectiveness of dabigatran compared with warfarin for stroke prevention in atrial fibrillation. *Ann Intern Med* 154: 1–11.
- Gage, B., Van Walraven, C., Pearce, L., Hart, R., Koudstaal, P., Boode, B. *et al.* (2004) Selecting patients with atrial fibrillation for anticoagulation: stroke risk stratification in patients taking aspirin. *Circulation* 110: 2287–2292.
- Glund, S., Stangier, J., Schmohl, M., De Smet M., Gansser, D., Lang, B. *et al.* (2013) A specific antidote for dabigatran: immediate, complete and sustained reversal of dabigatran induced anticoagulation in healthy male volunteers. *Circulation* 128: A17765
- Harper, P., Young, L. and Merriman, E. (2012) bleeding risk with dabigatran in the frail elderly. *N Engl J Med* 366: 864–866.
- Holster, I., Valkhoff, V., Kuipers, E. and Tjwa, E. (2013) New oral anticoagulants increase risk for gastrointestinal bleeding: a systematic review and meta-analysis. *Gastroenterology* 145:105–112.e15
- Husari, A., Beydoun, A., Sheik Ammar, A., Maakaron, J. and Taher, A. (2013) the untold story of dabigatran etexilate: alveolar hemorrhage in an elderly patient with interstitial pulmonary fibrosis. *J Thromb Thrombolysis* 35: 81–82.
- Jacobs, J. and Stessman, J. (2011) New anticoagulant drugs among elderly patients. Is caution necessary? Comment on ‘the use of dabigatran in elderly patients’. *Arch Intern Med* 171: 1287–1288.
- Larsen, T., Rasmussen, L., Skjoth, F., Due, K., Callreus, T., Rosenzweig, M. *et al.* (2013) Efficacy and safety of dabigatran etexilate and warfarin in ‘real-world’ patients with atrial fibrillation: a prospective nationwide cohort study. *J Am Coll Cardiol* 61: 2264–2273.
- Legrand, M., Mateo, J., Aribaud, A., Ginisty, S., Eftekhari, P., Huy, P. *et al.* (2011) The use of dabigatran in elderly patients. *Arch Intern Med* 171: 1285–1286.
- Southworth, M., Reichman, M. and Unger, E. (2013) Dabigatran and postmarketing reports of bleeding. *N Engl J Med* 368: 1272–1274.
- Stollberger, C. and Finsterer, J. (2012a) Concerns about studies investigating new anticoagulant drugs for stroke prevention in atrial fibrillation. *J Neurol* 259: 168–169.
- Stollberger, C. and Finsterer, J. (2012b) Concerns regarding the use of dabigatran for stroke prevention in atrial fibrillation. *Pharmaceuticals* 5: 155–168.
- Tsivgoulis, G., Kerasnoudis, A., Krogias, C., Vadikolias, K., Meves, S., Heliopoulos, I. *et al.* (2012) Clopidogrel load for emboli reduction in patients with symptomatic carotid stenosis undergoing urgent carotid endarterectomy. *Stroke* 43: 1957–1960.
- Tsivgoulis, G., Stamboulis, E., Sharma, V., Heliopoulos, I., Voumvourakis, K., Teoh, H. *et al.* (2010) Multicenter external validation of the ABCD2 score in triaging TIA patients. *Neurology* 74: 1351–1357.
- Tsivgoulis, G., Stamboulis, E., Sharma, V., Heliopoulos, I., Voumvourakis, K., Teoh, H. *et al.* (2011) Safety of transcranial doppler ‘bubble study’ for identification of right to left shunts: an international multicentre study. *J Neurol Neurosurg Psychiatry* 82: 1206–1208.
- Wann, L., Curtis, A., January, C., Ellenbogen, K., Lowe, J., Estes, N., III *et al.* (2011) 2011 ACCF/AHA/HRS focused update on the management of patients with atrial fibrillation (updating the 2006 guideline): a report of the American College of Cardiology

Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 123: 104–123.

Weimar, C., Hohnloser, S., Eikelboom, J. and Diener, H. (2012) Preventing cardioembolic stroke in atrial fibrillation with dabigatran. *Curr Neurol Neurosci Rep* 12: 17–23.

Wychowski, M. and Kouides, P. (2012) Dabigatran-induced gastrointestinal bleeding in an elderly patient

with moderate renal impairment. *Ann Pharmacother* 46: e10.

Zhao, L., Barlinn, K., Sharma, V., Tsivgoulis, G., Cava, L., Vasdekis, S. *et al.* (2011) Velocity criteria for intracranial stenosis revisited: an international multicenter study of transcranial doppler and digital subtraction angiography. *Stroke* 42: 3429–3434.

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