Safety and efficacy of dabigatran versus warfarin in patients undergoing catheter ablation of atrial fibrillation: a systematic review and meta-analysis

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ABSTRACT

Background Dabigatran etexilate, a new thrombin inhibitor, has been shown to be comparable to warfarin in patients with atrial fibrillation (AF). However, there is a limited body of evidence on the efficacy and safety of using dabigatran among patients undergoing AF catheter ablation.

Objective A random effects meta-analysis was performed of controlled trials comparing dabigatran and warfarin in paroxysmal/persistent AF patients undergoing catheter ablation.

Methods Data sources included Medline, Embase, and Cochrane (from inception to April 2013). Three independent reviewers selected studies comparing warfarin to dabigatran. Descriptive and quantitative information was extracted from each selected study, regarding periprocedural all cause mortality, thromboembolic events and major bleeding, as well as modalities of periprocedural anticoagulation bridging.

Results After a detailed screening of 228 search results, 14 studies were identified enrolling a total of 4782 patients (1823 treated with dabigatran and 2959 with warfarin). No deaths were reported. No significant differences were found between patients treated with dabigatran and warfarin as regards thromboembolic events (0.55% dabigatran vs 0.17% warfarin; risk ratios (RR)=1.78, 95% CI 0.66 to 4.80; p=0.26) and major bleeding (1.48% dabigatran vs 1.35% warfarin; RR=1.07, 95% CI 0.51 to 2.26; p=0.86). No difference was found between the 110 mg twice daily and 150 mg twice daily dabigatran dosages concerning major bleeding (0% vs 1.62%, respectively; RR=0.19, 95% CI 0.01 to 3.18; p=0.25) and thromboembolism (0% vs 0.40%, respectively; RR=0.72, 95% CI 0.04 to 12.98; p=0.82).

Conclusions In the specific setting of AF catheter ablation, this first pooled analysis suggests that patients treated with dabigatran have a similar incidence of thromboembolic events and major bleeding compared to warfarin, with low event rates overall.

INTRODUCTION

Atrial fibrillation (AF) is the most prevalent sustained arrhythmia and its prevalence is likely to rise steeply until 2050.[1] Stroke and systemic embolism are among the most feared complications of AF and can be effectively tackled by anticoagulation.[2]

Catheter ablation is currently recommended (class IIa, level of evidence C) as an interventional alternative for the treatment of patients with AF having symptomatic recurrences despite antiarrhythmic therapy.[3] Over the last 13 years this has become a very commonly performed procedure for the treatment of symptomatic AF patients.[4]

Rigorous anticoagulation in the setting of AF catheter ablation has been demonstrated to be of prime importance. The recent large phase III trials involving the use of novel oral anticoagulants[5–7] confirmed the non-inferiority, and even superiority in some cases, of dabigatran, rivaroxaban, and apixaban compared to warfarin in AF patients. However, since a planned AF catheter ablation procedure was listed as an exclusion criteria in those trials, the efficacy and safety results cannot be extended to that setting. The 2012 Expert Consensus Statement on the management of patients with AF, by the Heart Rhythm Society, European Heart Rhythm Association, and European Cardiac Arrhythmia Society,[8] highlights the limited clinical experience with the new anticoagulants in AF catheter ablation. Thus, even though dabigatran is being widely used and has been in vogue longer than the other new agents, strong evidence towards its utilisation in patients undergoing AF ablation is lacking. Further, the presence of controversial results[9] in controlled trials with warfarin has led cardiologists to question its safety and efficacy.

We therefore aimed to systematically evaluate, using a meta-analysis, all evidence concerning the use of dabigatran versus warfarin in catheter ablation for AF. The main objectives of this study were: (1) evaluate the efficacy and safety of dabigatran compared to warfarin; (2) determine whether there were significant differences between the 110 mg twice daily and 150 mg twice daily dosages of dabigatran; and (3) study the management of periprocedural bridging anticoagulation.

METHODS
Data sources and search strategy

We performed a search on Medline (via Ovid and PubMed), Embase, and Cochrane (from inception to 13 April 2013) databases using the following search string: "atrial fibrillation" AND "ablation" AND "dabigatran".

The reference lists of the accessed full text articles were further researched for sources of potential information relevant to this analysis. Experts in the field were contacted to ensure that all important studies in this area were covered. Abstract authors in

congresses were also contacted by email in order to retrieve additional information. The databases were reassessed before the completion of the manuscript to find if any of the included abstracts had been published as full text meanwhile.

Inclusion and exclusion criteria

The population, intervention, comparison, and outcome approach was used for conducting the meta-analysis.[10] The population of interest included patients with AF. The intervention was catheter ablation of AF and the associated periprocedural anticoagulation. Comparisons were performed between the following groups: warfarin versus dabigatran; dabigatran 110 mg twice daily vs 150 mg twice daily. The primary outcomes were: major bleeding, thromboembolism, and all cause mortality. The presence of minor bleeding, when reported, was also assessed.

Only controlled trials (full text articles or conference abstracts) of patients undergoing catheter ablation of AF and treated either with warfarin or dabigatran before the procedure were selected.

The minimum necessary follow-up for study inclusion was until discharge after the procedure. Additionally, to be included, studies needed to provide information on assessment of all three major clinical outcome parameters: major bleeding, thromboembolism, and death.

The following exclusion criteria were defined: trials with no comparator (ie, warfarin), namely observational studies including only patients treated with dabigatran; starting of dabigatran treatment only after catheter ablation; and evaluation of efficacy restricted to laboratory or imaging end points.

To ensure that trials met the prespecified inclusion criteria, search results were reviewed by three investigators (RP, AB, BC), who needed to be in agreement for study selection.

Data extraction and presentation for the preparation of this manuscript followed the recommendations of the PRISMA group.[11]

Study quality was formally evaluated using the Delphi Consensus criteria for randomised controlled trials[12] and a modified Newcastle–Ottawa Quality Assessment Scale for Case Control Studies[13] by three reviewers (RP, AB, BC). An agreement, between the three reviewers was mandatory for the final classification of studies.

End point definition for meta-analysis

Classification of bleeding was based on previous reports and suggested recommendations.[14] The following end points were defined for the generation of forest plots on meta-analysis.

The primary end points were:
1. All cause periprocedural death
2. Thromboembolism—a composite of stroke, transient ischaemic attack (TIA), systemic or pulmonary embolism. Asymptomatic cerebral embolism detected on routine or protocol MRI or CT (ie, imaging end points with no clinical manifestation) was not included in the analysis.
3. Major bleeding—comprising cardiac tamponade, bleeding necessitating intervention or transfusion, massive haemoptysis, haemothorax, retroperitoneal bleeding or any other life-threatening bleed leading to prolongation of hospitalisation.

Secondary end point was:
1. Minor bleeding—defined as puncture site bleeding, thigh ecchymosis or haematoma, pericardial effusion with no haemodynamic compromise, minor gastrointestinal bleeding, epistaxis or any bleeding treated conservatively with no need for transfusion, surgery or prolonged hospitalisation.

Assessment of periprocedural bridging of anticoagulation

The following data were extracted for assessing periprocedural bridging anticoagulation: periprocedural warfarin regimen (uninterrupted drug or discontinuation); timing of dabigatran interruption and restart; target activated clotting time (ACT).

Statistical analysis

Data were pooled using random effects, according to the Mantel–Haenszel model, through Review Manager (RevMan), V.5.1. (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011). The measurement of treatment effect was performed using risk ratios (RR) and 95% CIs. Pairwise comparisons were performed for all end points between patients treated with dabigatran and warfarin, and a separate sub-analysis (sensitivity analysis) was performed among patients treated with dabigatran, according to the dosage mentioned in the trials (150 mg twice daily vs 110 mg twice daily). Sensitivity analysis was also performed restricting the analysis of data to: trials whose patients were treated with uninterrupted warfarin, prospective studies, investigations published as full text articles, studies whose follow-up was at least 30 days, and studies in which five of the nine items on the Delphi Consensus criteria for randomised controlled trials and a modified Newcastle–Ottawa Quality Assessment Scale for case–control studies were deemed satisfactory.

Statistical heterogeneity on each outcome of interest was assessed and quantified using the Cochran Q test and the I^2 statistic, respectively. The presence of publication bias was evaluated by the use of funnel plots.

RESULTS
Search results

Overall, 228 entries were retrieved for title and abstract analysis. Of these, 169 were excluded as they did not meet inclusion criteria for the meta-analysis. The remaining 59 results were carefully screened, and after analysis of the full text (in the case of journal articles), only 14 studies (nine full text papers[9] [15–22] and five conference abstracts[23–27]) were deemed adequate for our review's purpose. The stepwise selection process is illustrated in figure 1. There was a good agreement between investigators on the inclusion of the selected trials.

Baseline data and the design of selected trials are summarised in tables 1 and 2. The final population for this meta-analysis was composed of 4782 patients (1823 treated with dabigatran and 2959 with warfarin). Table 3 illustrates the assessment of the included studies through the Delphi criteria for randomised studies and the Newcastle–Ottawa Scale for non-randomised case–control studies.

The observed I^2 values showed a low to moderate heterogeneity in the main end point comparisons ($I^2=0$ for stroke and 41% for major bleeding).

Efficacy and safety of dabigatran versus warfarin

The main efficacy and safety outcomes (prevention of embolism and major bleeding) observed in the comparison between dabigatran and warfarin are displayed in figure 2 and table 4. The funnel plot to ascertain publication bias is shown in figure 3.

Death and thromboembolism

No deaths were observed in any of the intervention groups. Thromboembolic events were reported in only 0.31% of patients (15 out of 4782) and no significant differences were found between dabigatran and warfarin: 0.55% vs 0.17%, respectively (RR=1.78, 95% CI 0.66 to 4.80; p=0.26).
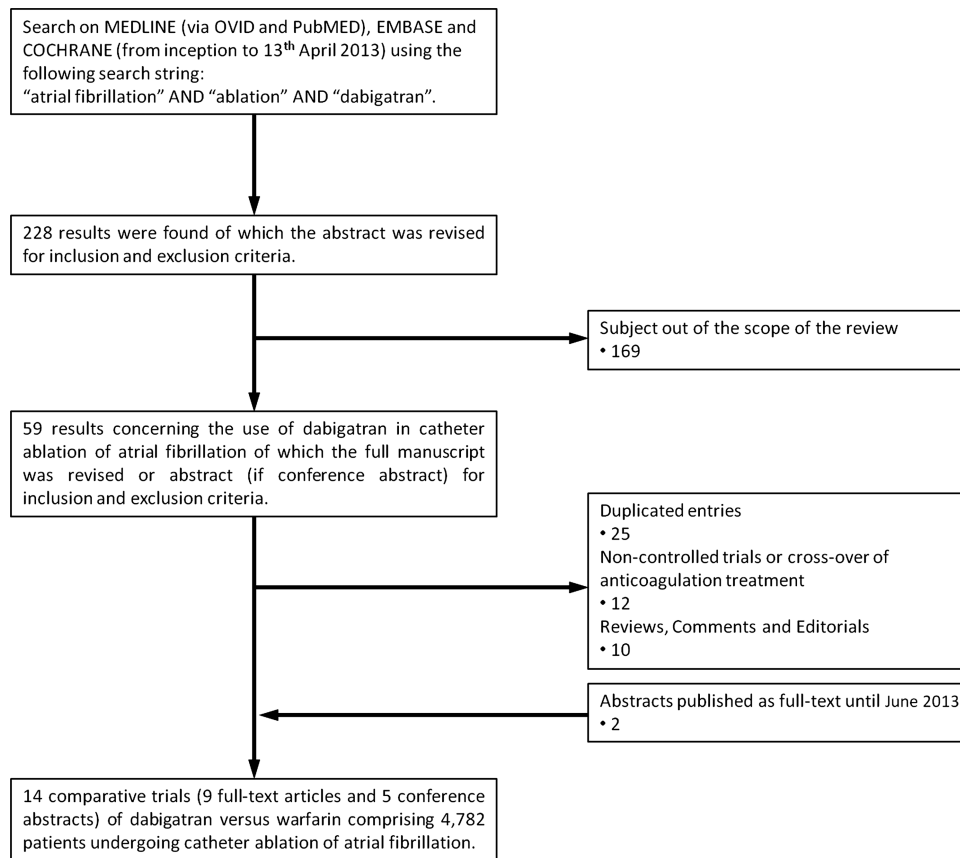
Figure 1 Flowchart diagram illustrating study selection.

Major bleeding

Among all 14 studies, 67 events (accounting for an overall 1.40% incidence) of major bleeding were reported, with no significant differences observed between the two treatment arms (1.48% dabigatran vs 1.35% warfarin; RR=1.07, 95% CI 0.51 to 2.26; p=0.86).

Minor bleeding

Information on minor bleeding was not reported in one of the selected studies.[24] In the remaining, comprising 4572 participants, 210 minor bleeding events (overall incidence 4.59%; 3.35% dabigatran vs 5.40% warfarin) were reported, with a relative risk reduction of 35% (95% CI 7 to 55%; p=0.02) in favour of dabigatran (figure 4).

Sensitivity analysis

Sensitivity analysis confirmed the lack of interference of uninterrupted warfarin, prospective studies, full text articles, studies whose follow-up was at least 30 days, and higher methodological quality studies (figures 5–7) in the overall results concerning the main end points: stroke and thromboembolism and major bleeding. However, as regards minor bleeding these analyses suggested a lack of significant differences.

Effect of dabigatran dosage: 150 mg twice daily vs 110 mg twice daily

Information on the dose of dabigatran used was available for 1392 patients (155 with 110 mg twice daily and 1237 with 150 mg twice daily). No significant differences were found between the two dosage groups (110 mg twice daily vs 150 mg twice daily, respectively) regarding major bleeding (0% vs 1.62%; RR=0.19, 95% CI 0.01 to 3.18; p=0.25) and thromboembolism (0% vs 0.40%; RR=0.72, 95% CI 0.04 to 12.98; p=0.82). Concerning minor bleeding, more events were observed with the 110 mg twice daily dosage: 9.03% vs 2.51% (RR=3.60, 95% CI 1.96 to 6.62; p<0.0001).

Management of periprocedural anticoagulation

The different periprocedural regimens used in patients treated with dabigatran are displayed in table 2. The timing of the first withheld dose ranged from the morning of procedure (in four studies) to 48 h before; the time interval for restarting ranged from 3–4 h (in six studies) to 24 h after ablation. In one study, uninterrupted dabigatran was used.[19]

One third of all strokes or TIAs were associated with suspension of dabigatran for ≥24 h before procedure (one stroke in Haines et al[16] and one stroke and one TIA in Rowley et al[27]). Additionally, of all stroke and TIA in patients treated with dabigatran, 50% was related to a later timing (≥12 h) for restarting the drug post-procedure (two strokes and two TIAs[16 27]). On the other hand, a higher incidence of major bleeding was reported by Lakkireddy et al,[9] where dabigatran was stopped only in the morning of the procedure and restarted 3 h post-procedure. Albeit suggesting a similar safety and efficacy profile, with non-inferiority versus warfarin, data concerning uninterrupted dabigatran results exclusively from one trial.[19]

Among the patients of the warfarin group, safety and efficacy outcomes were similar irrespective of whether warfarin was continued or interrupted.

In addition, target ACT during procedure was 300–350 s in most studies, >350 s in five,[9 15 19–21] and 250–300 s in one.[26] A higher value for target ACT[9 15 19–21] was not associated with

Table 1 Baseline characteristics of included studies

	Bassiouny et al[15]	Bernard et al[23]	Haines et al[16]	Ichiki et al[24]	Kaseno et al[17]	Kim et al[18]	Lakkireddy et al[9]	Maddox et al.[19]	Mendoza et al[25]	Nin et al[20]	Pavaci et al[26]	Rowley et al[27]	Snipelisky et al[21]	Yamaji et al[22]
Source type	Journal article	Conference abstract	Journal article	Conference abstract	Journal article	Journal article	Journal article	Journal article	Conference abstract	Journal article	Conference abstract	Conference abstract	Journal article	Journal article
Study design	Prospective, monocentric registry	Retrospective	Multicentric, retrospective, case-match analysis	Prospective, non-randomised	Retrospective	Retrospective	Multicentric, prospective, non-randomised	Retrospective	Retrospective	Prospective, randomised	Retrospective, case-match analysis	Retrospective	Retrospective	Retrospective, non-randomised and randomised*
Paroxysmal AF	57% D 55% W	46% D 50% W	53% D 48% W	53%	83% D 55% W	53% D 48% W	57% D 57% W	63% D 57% W	NA	76% D 71% W	NA	NA	68% D 46% W	65% D 62% W
Age	58.6 D 62.7 W	62.7 D 67.3 W	60.2 D 59.7 W	n.s.	59 D 62 W	61 D 61 W	60.4 D 60.3 W	62.3 D 62.5 W	62.9 D 64.0 W	61 D 61 W	NA Case-matched	63±10 similar	60.6 D 64.6 W	60 D 61 W
♀ Gender	25% D 26.6% W	NA	26% D 31% W	NA	25% D 21% W	20% D 26% W	21% D 21% W	24% D 33% W	10% D 12% W	16% D 20% W	NA Case-matched	NA	19.4% D 25.6% W	25% D 24% W
Estimated thrombo-embolic risk	$CHADS_2$ Score=0 42.6% D 29.1% W Score=1 37.0% D 41.6% W Score ≥2 20.5% D 29.4% W	CHA_2DS_2-VASc 2.00 D 2.68 W	CHA_2DS_2-VASc 1.6±1.3 D 1.9±1.4 W	Values NA ns differences between treatment groups	$CHADS_2$ Score=0 61% D 45% W Score=1 31%D 41% W Score ≥2 8% D 14% W	CHA_2DS_2-VASc 1.6±1.3 D 1.7±1.3 W	$CHADS_2$ Score=0 35% D 40% W Score=1 43% D 41% W Score ≥2 23% D 19% W CHA_2DS_2-VASc 1.6±1.4 D 1.5±1.3 W	$CHADS_2$ 0.92±0.88 D 0.92±0.85 W CHA_2DS_2-VASc 1.73±1.45 D 1.69±1.33 W	$CHADS_2$ 1.32 D 1.29 W	$CHADS_2$ Score ≤1 82% D 80% W Score=1 11% D 13% W Score ≥2 4% D 11% W	NA	$CHADS_2$ 1.3±1	$CHADS_2$ 0.80 D 1.16 W	$CHADS_2$ Score=0 36% D 33% W Score=1 40% D 38% W Score ≥2 24% D 29% W CHA_2DS_2-VASc 1.8±1.6 D 1.7±1.6 W
Estimated bleeding risk	NA	NA	NA	NA	HAS-BLED 0.5±0.7 D 0.6±0.6 W	HAS-BLED 1.0±0.9 D 1.1±0.9 W	HAS-BLED 1.2±0.9 D 1.1±0.9 W	NA	HAS-BLED 1.47 D 1.63 W	NA	NA	NA	NA	NA
LV ejection fraction	55% D 55% W	60% D 58% W	56% D 57% W	NA	64% D 63% W	58% D 57% W	56% D 56% W	53% D 54% W	NA	61% D 62% W	NA	NA	NA	60% D 60% W
CKD/kidney function	Creat 0.9 mg/dL D 0.9 mg/dL W	Creat 1.0 mg/dL D 1.3 mg/dL W	Creat clearance 93 ml/min D 93 ml/min W	NA	Creat clearance 97 ml/min D 98 ml/min W	Creat 0.9 mg/dL D 0.9 mg/dLW	CKD 1% D 2% W	Creat 1.0 mg/dL D 1.1 mg/dL W	NA	Creat 0.9 mg/dL D 0.9 mg/dL W	NA	NA	NA	Exclusion of patients with renal clearance < 30 mL/min

The first 291 patients were assigned to interrupted and non-interrupted warfarin in a non-randomised fashion and the last 212 patients were randomised to either uninterrupted warfarin or dabigatran.

AF, atrial fibrillation; CKD, chronic kidney disease; Creat, creatinine; D, dabigatran; LV, left ventricle; NA, not available; W, warfarin.

Table 2 Description of periprocedural anticoagulation

	Bassiouny et al[15]	Bernard et al[23]	Haines et al[16]	Ichiki et al[24]	Kaseno et al[17]	Kim et al[18]	Lakkireddy et al[9]	Maddox et al[19]	Mendoza et al[25]	Nin et al[20]	Pavaci et al[26]	Rowley et al[27]	Snipelisky et al. [21]	Yamaji et al[22]
Patients treated with dabigatran	376	155	222	30	110	191	145	212	60	45	27	113	31	106
Dabigatran dosage	150 mg twice daily	NA	150 mg twice daily*	NA	110 mg twice daily	150 mg twice daily	150 mg twice daily	150 mg twice daily	150 mg twice daily	110 mg twice daily	NA	NA	150 mg twice daily	110 mg twice daily in 36 150 mg twice daily in 70
Timing of first held dose of dabigatrain	Morning of the day of the procedure or the night before	24 h	≤12 h in 35 12–24 h in 29 24–48 h in 102 >48 h in 18 Unknown in 18	Morning of procedure	Morning of procedure	Night before procedure	Morning of procedure	Uninterrupted	Morning of procedure	Morning of the day before procedure	NA	Day before procedure	Morning of procedure	Morning of the day of the procedure
Time interval for restarting after procedure	After arousal from anesthesia/ sedation	Within 24 h	≤6 h in 116 6–24 h in 83 >24 h in 1 Unknown in 2	NA	Morning after procedure	4 h	3 h	Uninterrupted	Immediately after sheath removal (144.3 min)	4 h after haemostasis at the puncture site	NA	> 24 h (day following)	Evening of procedure	Single dose, 3 h after the completion of the procedure
Patients treated with warfarin	623	44	222	180	101	572	145	251	58	45	27	169	125	397
Timing of first held dose of warfarin	Uninterrupted	Uninterrupted	≤12 h in 74 12–24 h in 88 24–48 h in 15 >48 h in 25	Uninterrupted	Uninterrupted	Uninterrupted	Uninterrupted	Uninterrupted	Uninterrupted	Morning of the day before procedure	Uninterrupted	Day before procedure	Evening prior to the procedure	Uninterrupted in 203 patients. Interrupted 48 h before in 194
Timing for restarting warfarin	Uninterrupted	Uninterrupted	Day of the procedure	Uninterrupted	Uninterrupted	Uninterrupted	Uninterrupted	Uninterrupted	Uninterrupted	4 h after haemostasis at the puncture site	Uninterrupted	Day after procedure	Evening of procedure	Day after procedure in patients who stopped warfarin
Target ACT (seconds) during procedure	350–450	NA	300–350 at least	NA	300–350	300–350	300–400	>350–400	300–350	300–400	250–300	NA	>350	300–350
Follow-up duration	1 month	1 month	Periprocedural/ hospital discharge	NA	At least 2 months	3 months	30 days	Periprocedural/ hospital discharge	1 month	2 weeks	NA	30 days	1 week	3 months

*Except for one elderly patient who took the 110 mg twice daily dose.
ACT, activated clotting time; NA, not available.

Table 3 Assessment of the quality of included studies: Delphi criteria for randomised studies and Newcastle–Ottawa Scale for non-randomised case-controls studies

Study	Assessment	Classification*
Bassiouny et al[15]	Adequate case definition; consecutive series of cases; adequate information concerning the selection and definition of controls; groups controlled for baseline characteristics; ascertainment of outpatient exposure to anticoagulants based on medical records both for cases and controls, and laboratory data for warfarin; patients not blinded to case-control status.	Attributable stars: 7
Bernard et al[23]	Adequate case definition; consecutive series of cases; controls were slightly older (3 years in average), had higher creatinine values (1.3 vs 1.0 mg/dL) and a higher CHA_2DS_2-VASc (2.68 vs 2.00); information concerning the selection and definition of controls.	Attributable stars: 3
Haines et al[16]	Adequate case definition; consecutive series of cases; hospital controls, obtained by computer list generation; groups controlled for most baseline characteristics, except for slight differences in congestive heart failure, more prevalent in the dabigatran group, and previous stroke, more prevalent in the warfarin group; a higher utilisation of concomitant aspirin was observed in dabigatran patients and heparin/low molecular weight heparin was more used in the warfarin treatment arm; ascertainment of outpatient exposure to anticoagulants based on medical records both for cases and controls, and laboratory data for warfarin; patients not blinded to case-control status.	Attributable stars: 6
Ichiki et al[24]	Adequate case definition; consecutive series of cases; adequate information concerning the selection and definition of controls; information concerning the selection and definition of controls.	Attributable stars: 4
Kaseno et al[17]	Adequate case definition; information concerning the selection and definition of controls; hospital controls; slight difference in baseline age (warfarin patients 3 years older), larger left atrial diameter (4 mm difference in average) and higher prevalence of persistent AF in the warfarin group, requiring additional substrate modification; ascertainment of outpatient exposure to anticoagulants based on medical records both for cases and controls, and laboratory data for warfarin; patients not blinded to case-control status.	Attributable stars: 4
Kim et al[18]	Adequate case definition; consecutive series of cases; adequate information concerning the selection and definition of controls; groups controlled for baseline characteristics, except for previous stroke, that was slightly more prevalent in the warfarin group; ascertainment of outpatient exposure to anticoagulants based on medical records both for cases and controls, and laboratory data for warfarin; close monitoring of all patients during the 3 month follow-up period after the procedure; patients not blinded to case-control status.	Attributable stars: 6
Lakkireddy et al[9]	Adequate case definition; consecutive series of cases in the dabigatran treatment arm; controls matched for age, sex and type of AF; groups controlled for baseline characteristics; ascertainment of outpatient exposure to anticoagulants based on medical records both for cases and controls, and laboratory data for warfarin; patients not blinded to case-control status.	Attributable stars: 6
Maddox et al[19]	Adequate case definition; consecutive series of cases; adequate information concerning the selection and definition of controls; groups controlled for most baseline characteristics, except for a slightly higher percentage of males in the dabigatran group; ascertainment of outpatient exposure to anticoagulants based on medical records both for cases and controls, and laboratory data for warfarin; patients not blinded to case-control status.	Attributable stars: 6
Mendoza et al[25]	Adequate case definition; consecutive series of cases; hospital controls; information concerning the selection and definition of controls.	Attributable stars: 4
Nin et al[20]	Randomisation performed; groups similar at baseline; eligibility criteria specified; point estimates and measures of variability presented for outcome measures; analysis of end points performed on an intention-to-treat basis.	Positive Delphi criteria: 5
Pavaci et al[26]	Adequate case definition; consecutive series of cases treated with dabigatran; case matched hospital controls considering age, gender, body mass index, creatinine values, left atrium dimensions and type of arrhythmia; information concerning the selection and definition of controls.	Attributable stars: 4
Rowley et al[27]	Adequate case definition; series of cases treated with dabigatran, no information if the patients were consecutive; no information concerning the selection and definition of controls; similar age and $CHADS_2$ score among treatment groups.	Attributable stars: 3
Snipelisky et al[21]	Adequate case definition; consecutive series of cases; adequate information concerning the selection and definition of controls; groups controlled for baseline characteristics, except for higher prevalence of persistent AF in the warfarin group; ascertainment of outpatient exposure to anticoagulants based on medical records both for cases and controls, and laboratory data for warfarin; patients not blinded to case-control status; all patients had evidence for a completed medication profile with reconciliation.	Attributable stars: 7
Yamaji et al[22]	Adequate case definition; consecutive series of patients assigned to treatment groups in a non-randomised fashion in the first part of the study and with randomisation to dabigatran or uninterrupted warfarin in the last 212 patients; adequate information concerning the selection and definition of controls; groups controlled for baseline characteristics; ascertainment of outpatient exposure to anticoagulants based on medical records both for cases and controls, and laboratory data for warfarin; close monitoring of all patients during the 3-month follow-up period after the procedure; patients not blinded to case-control status.	Attributable stars: 7

*Number of criteria met out of a total of nine.
AF, atrial fibrillation.

a lower incidence of thromboembolic events. Furthermore, in the investigation by Lakkireddy et al[9] a higher rate of cardiac tamponade in dabigatran treated patients (9/145) was observed. Importantly, a 3.7% rate of stroke was observed in the single study featuring a target ACT of 250–300 s.[26] However, due to the low number of participants, the possibility of a false positive association cannot be excluded.

DISCUSSION

The low rate of thromboembolic complications and major bleeding seen with dabigatran (which was also similar to that observed with warfarin) seems to provide favourable support for its use, as an alternative to warfarin, in the setting of

catheter ablation of AF. These results add important information on the use of dabigatran in this setting. They also serve to potentially alleviate some of the concerns raised by the rather unfavourable results in earlier studies (2.1% stroke or TIA and 6.2% major bleeds),[9] suggesting that dabigatran significantly increased the risk of bleeding or thromboembolic complications compared with uninterrupted warfarin therapy.

A very low rate of stroke and thromboembolic events was found in this meta-analysis among patients treated with dabigatran (0.55%), similar to what has been found in a recent analysis of Medicare beneficiaries (0.6–0.9%).[28] A lower, but not significantly different, prevalence of embolism was found in the warfarin arm of this meta-analysis (0.17%), composed mainly of

A   Stroke and Thromboembolism

Study or Subgroup	Dabigatran Events	Total	Warfarin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Bassiouny 2013	1	376	1	623	12.9%	1.66 [0.10, 26.41]
Bernard 2013	0	155	0	44		Not estimable
Haines 2012	2	222	0	222	10.7%	5.00 [0.24, 103.56]
Ichiki 2012	0	30	0	180		Not estimable
Kaseno 2012	0	110	0	101		Not estimable
Kim 2012	0	191	0	572		Not estimable
Lakkireddy 2012	3	145	0	145	11.3%	7.00 [0.36, 134.32]
Maddox 2013	1	212	0	251	9.7%	3.55 [0.15, 86.67]
Mendoza 2012	0	60	1	58	9.7%	0.32 [0.01, 7.76]
Nin 2012	0	45	1	45	9.8%	0.33 [0.01, 7.97]
Pavaci 2012	1	27	0	27	9.9%	3.00 [0.13, 70.53]
Rowley 2012	2	113	2	169	26.0%	1.50 [0.21, 10.46]
Snipelsky 2012	0	31	0	125		Not estimable
Yamaji 2012	0	106	0	397		Not estimable
Total (95% CI)		**1823**		**2959**	**100.0%**	**1.78 [0.66, 4.80]**
Total events	10		5			

Heterogeneity: Tau² = 0.00; Chi² = 3.78, df = 7 (P = 0.80); I² = 0%
Test for overall effect: Z = 1.14 (P = 0.26)

B   Major Bleeding

Study or Subgroup	Dabigatran Events	Total	Warfarin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Bassiouny 2013	4	376	8	623	15.9%	0.83 [0.25, 2.73]
Bernard 2013	2	155	2	44	9.6%	0.28 [0.04, 1.96]
Haines 2012	3	222	3	222	12.1%	1.00 [0.20, 4.90]
Ichiki 2012	4	30	4	180	14.4%	6.00 [1.59, 22.71]
Kaseno 2012	0	110	2	101	5.0%	0.18 [0.01, 3.78]
Kim 2012	4	191	12	572	16.7%	1.00 [0.33, 3.06]
Lakkireddy 2012	9	145	1	145	8.8%	9.00 [1.16, 70.13]
Maddox 2013	1	212	3	251	7.8%	0.39 [0.04, 3.77]
Mendoza 2012	0	60	0	58		Not estimable
Nin 2012	0	45	0	45		Not estimable
Pavaci 2012	0	27	0	27		Not estimable
Rowley 2012	0	113	1	169	4.5%	0.50 [0.02, 12.09]
Snipelsky 2012	0	31	0	125		Not estimable
Yamaji 2012	0	106	4	397	5.3%	0.41 [0.02, 7.62]
Total (95% CI)		**1823**		**2959**	**100.0%**	**1.07 [0.51, 2.26]**
Total events	27		40			

Heterogeneity: Tau² = 0.54; Chi² = 15.19, df = 9 (P = 0.09); I² = 41%
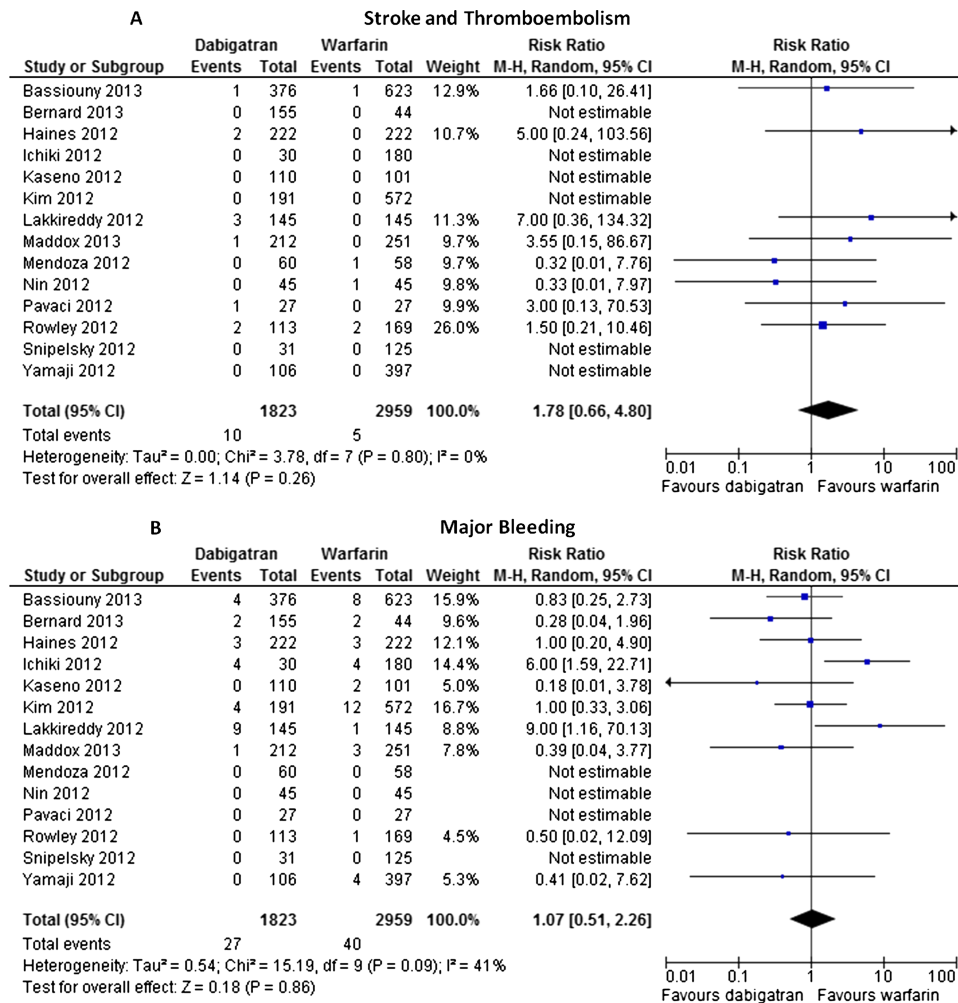Test for overall effect: Z = 0.18 (P = 0.86)

Figure 2 Main efficacy and safety outcomes of the comparison of dabigatran versus warfarin among patients with atrial fibrillation treated with catheter ablation. (A) Stroke and thromboembolism. (B) Major bleeding. M-H, Mantel–Haenszel.

patients with uninterrupted treatment. This value is similar to the one described by Hussein *et al*[29] in patients with uninterrupted warfarin. Therefore, we think that despite showing similar results compared to warfarin in this meta-analysis (and presenting values for thromboembolic complications similar to what has been reported in large registries of patients using antivitamin K agents[28]), validation of these results in future randomised controlled trials with blinded analysis may be justified. Furthermore, the use of uninterrupted dabigatran may also merit assessment, taking into account the promising results of the recently available study with this treatment regimen.[19]

The proportion of patients referred for AF ablation who are on longstanding dabigatran therapy is progressively increasing. This is likely to pose new challenges for the practising cardiologist, including the question of performing the procedure without discontinuation of dabigatran. The pooled data in this study from a large sample of patients provides an opportunity to address some of these issues.

In this meta-analysis comprising 14 controlled trials, dabigatran performed similarly to warfarin with regard to major bleeding and thromboembolism. Moreover, no deaths were observed in any of the treatment strategies. These results are in agreement with the favourable profile that was observed in an early observational non-controlled trial by Winckle *et al*.[30] Furthermore, a recent analysis of the US Food and Drug Administration (FDA) Mini-Sentinel database for the period from 19 October 2010

(the date of dabigatran approval) to 31 December 2011, found that bleeding rates associated with dabigatran use during the period of interest did not appear to be higher than those associated with warfarin.[31]

Though the present analysis suggests a lower rate of minor bleeding with dabigatran, there were pronounced differences in the reporting of this end point across the different studies. Furthermore, on sensitivity analysis these results did not remain significant. Thus, while this result needs to be interpreted with caution, it seems, that at the very least, dabigatran is unlikely to be inferior to warfarin in this regard.

No significant differences in major bleeding and thromboembolism were observed between the two assigned dabigatran dosages. However, the low number of patients in each group (resulting from under-reporting of the dosage used in most selected studies), and the low rate of observed events, limit the extent to which firm conclusions can be drawn. The suggestion of less frequent minor bleeding with the 150 mg twice daily dosage is hard to interpret due to the differences in reporting of this end point and in sample size.

The various transition regimens used in patients treated with dabigatran, and the low number of observed events in each of those, renders difficult the task of establishing an ideal transition regimen in this setting. However, the great inter- and sometimes intra-study variability notwithstanding, certain factors are likely to be important for decision making.

Table 4 Comparison of endpoints across studies

	Bassiouny et al[15]	Bernard et al[23]	Haines et al[16]	Ichiki et al[24]	Kaseno et al[17]	Kim et al[18]	Lakkireddy et al[9]	Maddox et al[19]	Mendoza et al[25]	Nin et al[20]	Pavaci et al[26]	Rowley et al.[27]	Snipelisky et al[21]	Yamaji et al[22]
Minor bleeding	7/376 D 16/623 W Groin haematoma 5/ 376 D 10/ 623 W GI bleed 1/376 D 2/623 W Minor haemoptysis 1 /623 W Epistaxis1/ 623 W PEff without tamponade 1/376 D 2/623 W	1/155 D 2/44 W	4/ 222 D 2/ 222 W Minor bleeding complications 2/ 222 D 1/ 222 W Vascular complication 2/222 D 1/222 W	NA	5/110 D 11/101 W Groin haematoma 5/110 D 11/101 W	5/191 D 19/572 W Groin haematoma 4/191 D 19/572 W PEff without tamponade 1/191 D	12/145 D 8/145 W Groin haematoma 6/145 D 5/145 W PEff without tamponade 6/145 D 4/145 W	1/212 D 3/251 W Groin haematoma 1/212 D 2/251 W Minor haemoptysis 1/251 W	1/60 D 1/58 W Groin haematoma 1/58 W GI bleed 1/60 D	9/45 D 20/45 W Rebleeding from puncture site 9/45 D 20/45 W	2/27 D 4/27 W Groin haematoma 2/27 D 4/27 W	5/113 D 33/169 W Non-life threatening vascular complications 5/113 D 33/169 W	6/31 D 21/125 W Haematoma 1/31 D 4/125 W Rebleeding 5/31 D 10/125 W Ecchymosis 7/125 W	2/106 D 11/397 W Groin haematoma 1/106 D 4/397 W PEff without tamponade 1/106 D 7/397 W
Major bleeding Retroperitoneal bleed 1/169 W	4/376 D 8/623 W PEff with need of pct 3/ D 7/ W Haemoptysis* 1/ W Cerebral bleeding 1/ D† 0	2/155 D 2/44 W 0/106 D 4/397 W Cardiac	3/222 D 3/222 W PEff with need of pct 2/222 D 2/222 W Other major bleeding 1/222 D 1/222 W tamponade 4/397 W	4/30 D 4/180 W PEff with need of pct 4/30 D 4/180 W	0/110 D 2/101 W Cardiac tamponade 2/101 W	4/191 D 12/572 W Cardiac tamponade 2/191 D 7/572 W Vascular		complications 2/191 D 5/572 W	9/145 D 1/145 W Cardiac tamponade 9/145 D 1/145 W	1/212 D 3/251 W Cardiac tamponade 1/212 D 2/251 W Retroperitoneal haematoma 1/251 W	0	0	0	0/113 D 1/169 W
Thrombo-embolism	1/376 D 1/623 W Stroke 1/623 W Pulmonary embolism 1/376 D	0	2/222 D ‡ 0/222 W Stroke 1/222 D TIA 1/222 D	0	0	0	3/145 D 0/145 W Stroke or TIA 3/145 D	1/212 D 0/251 TIA 1/212 D	0/60 D 1/58 W Stroke 1/58 W	0/45 D 1/45 W Mesenteric thrombosis 1/45 W	1/27 D 0/27 W Stroke 1/27 D	2/113 D 2/169 W Stroke 1/113 D 1/169 W TIA 1/113 D Pulmonary embolism 1/169 W	0	0

*Requiring transfusion.
†Patient with a cerebral cavernous malformation.
‡The patients with stroke stopped dabigatran 36 h before the procedure and the patient with TIA restarted the drug only 17 h after the procedure.
D, dabigatran; GI, gastrointestinal; NA, data not available; pct, pericardiocentesis; PEff, pericardial effusion; punct, puncture; TIA, transient ischaemic attack; W, warfarin.

Figure 3 Funnel plots representing the studies used in the assessment of: (A) stroke and thromboembolism; and (B) major bleeding. The inverted and symmetrical funnel aspect can be observed for the assessed end points, with 95% of the studies lying within the confidence limit lines. This suggests that publication bias is not present among the selected studies for the meta-analysis.
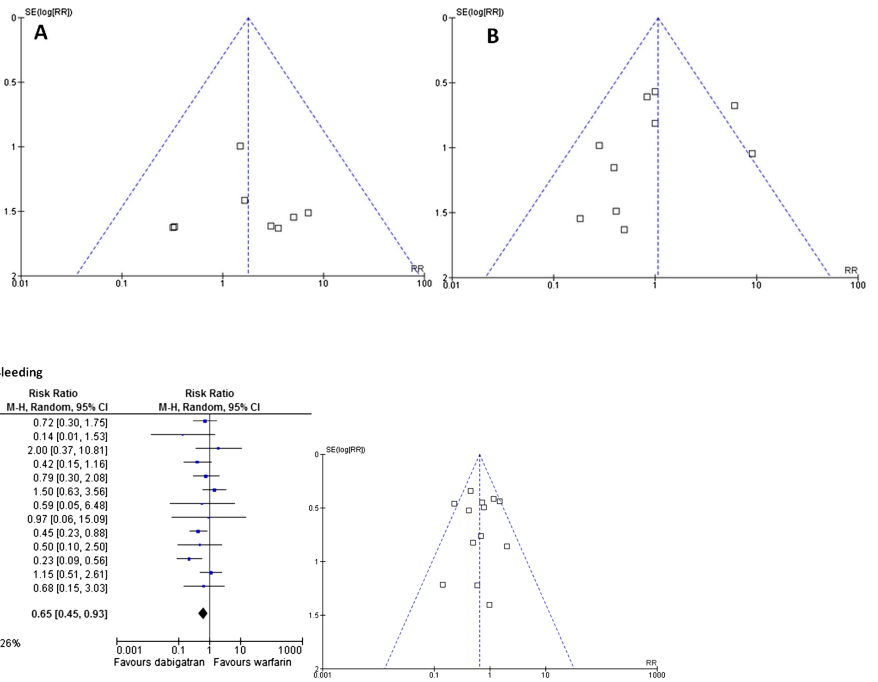

Figure 4 Incidence of minor bleeding among patients treated with dabigatran or warfarin. (A) Forest plot. (B) Funnel-plot. M-H, Mantel–Haenszel.
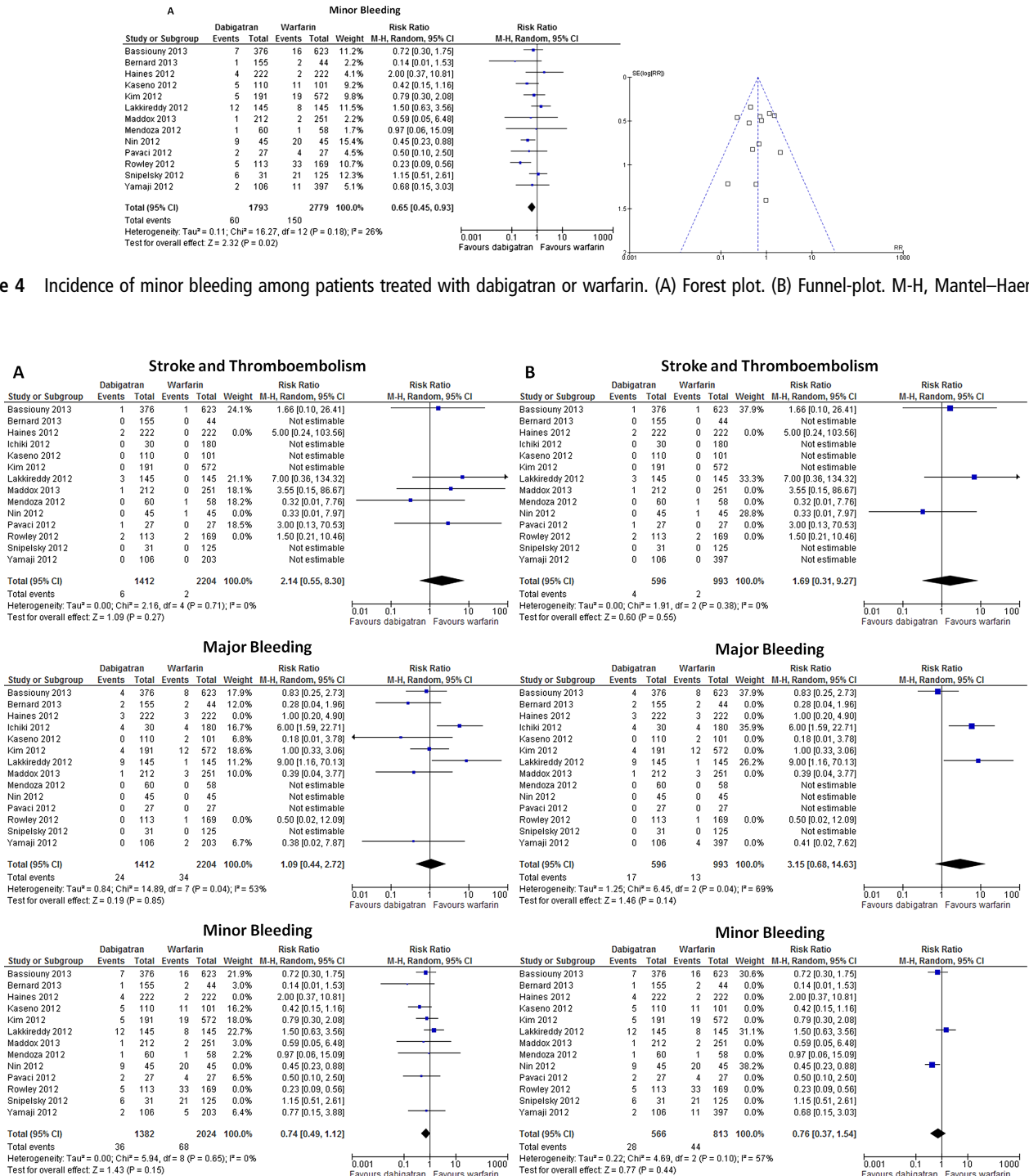

Figure 5 Forest plot illustrating the sensitivity analysis restricting data to: (A) trials whose patients were treated uninterrupted warfarin; and (B) prospective studies. M-H, Mantel–Haenszel.
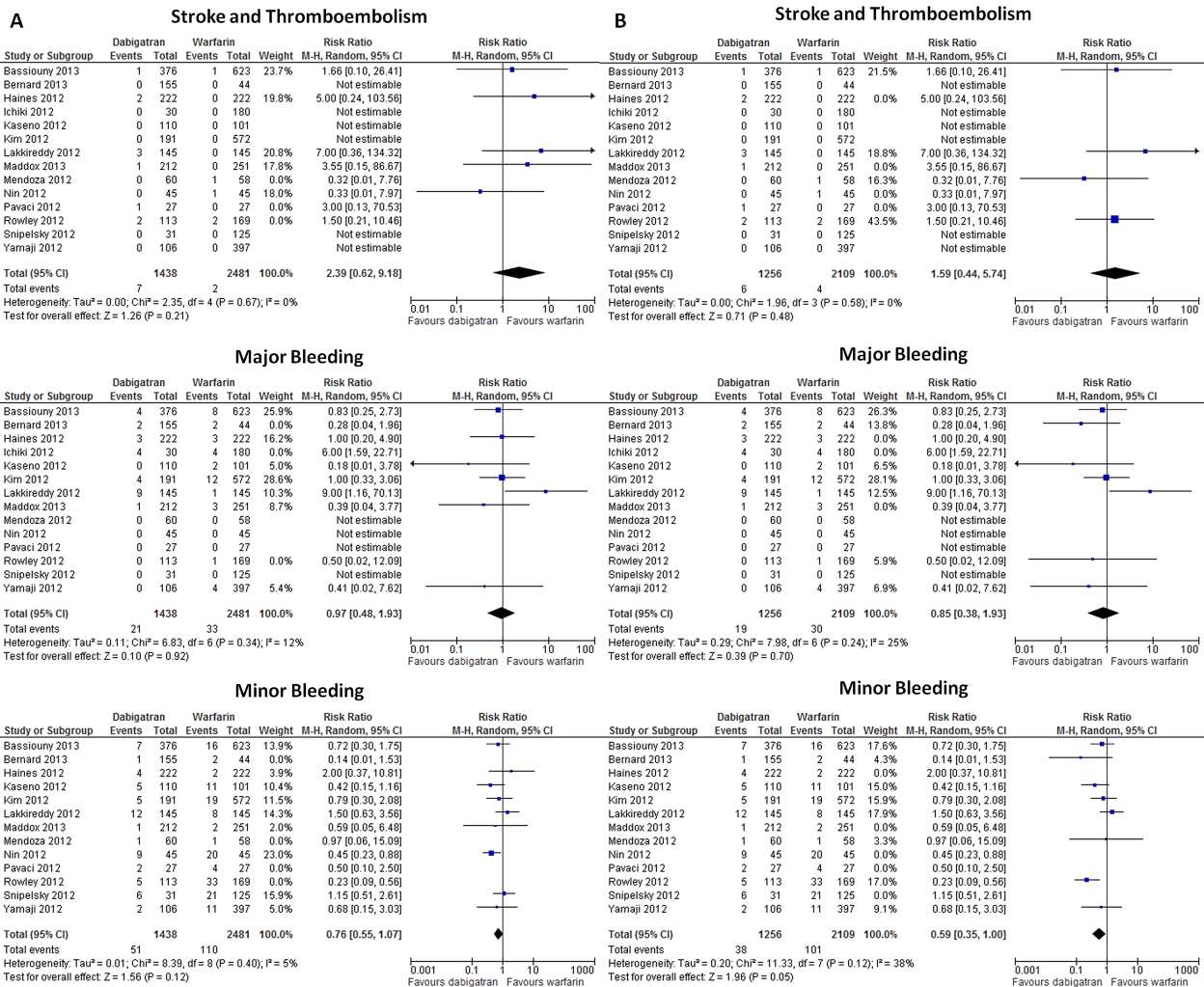
Figure 6 Forest plot illustrating the sensitivity analysis restricting data to: (A) investigations published as full text articles; and (B) studies whose follow-up was at least 30 days. M-H, Mantel–Haenszel.

The timing for drug interruption before the procedure must take into account the patient's renal function, as 80% of the drug is excreted by this pathway.

In patients with normal renal clearance, the best option may be drug suspension on the morning of the procedure, or the night before, but always <24 h before the procedure.

If renal function is compromised, the drug should probably be interrupted sooner, depending on the degree of renal dysfunction.

There may be a rationale for restarting dabigatran 3–4 h after assuring haemostasis, considering its short half-life and rapid onset of action.

The target ACT during catheter ablation in patients treated with dabigatran should be between 300–350 s (similar to warfarin), as no additional benefits were found for higher values.

Finally, as there seems to be no inherent advantage of any of the studied dabigatran dosages, the creatinine clearance and bleeding risk (HAS-BLED score) should be taken into account for deciding the dosage to be used.

LIMITATIONS

Important strengths of this study include the consistent reporting for thromboembolism (almost absent heterogeneity, $I^2=0\%$) across studies. However, there are certain limitations, inherent to any meta-analysis.
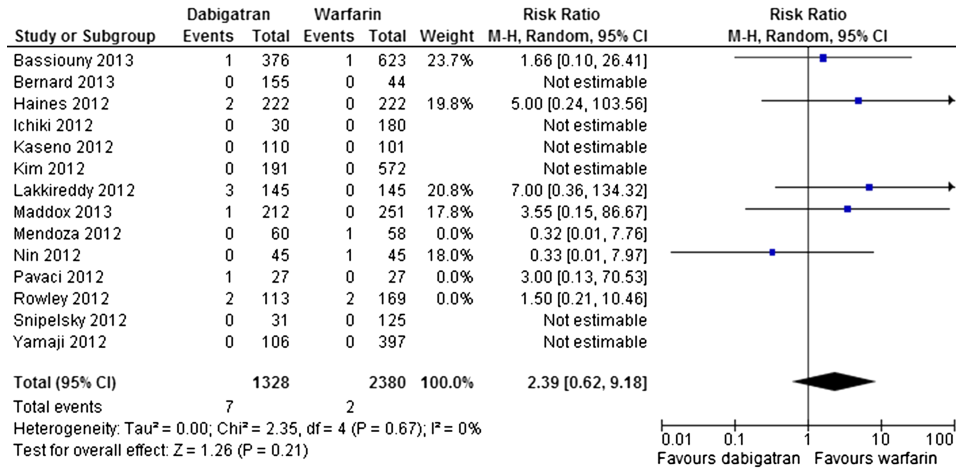
First, heterogeneity was observed regarding major bleeding ($I^2=41\%$; moderate heterogeneity). This may be explained by the pronounced diversity in ablation strategy, anticoagulation regimen, intraprocedural use of heparin, and follow-up between the incorporated studies. However, heterogeneity was low ($I^2=12\%$) in the sensitivity analysis including only higher methodological quality studies, which confirms the small and similar incidence of major bleeding in both treatment arms already suggested by the forest plot that included all studies.

Secondly, as already highlighted, certain comparisons are limited by the low number of subjects and low event rates.

Thirdly, in some cases of abstract related data, even with the best attempts to gather information by directly contacting the authors, some data remained incomplete. However, these were mainly with regard to minor bleeding (a secondary end point) and details concerning periprocedural drug transition; hence, missing data are unlikely to have significantly affected the primary results of the analysis.

Fourthly, only a minority of trials was randomised or prospective and a blinded analysis and/or central adjudication of end points was performed in none (ie, the higher level of data quality). Therefore, these data must be considered preliminary and interpreted with some caution.

Stroke and Thromboembolism

Study or Subgroup	Dabigatran Events	Dabigatran Total	Warfarin Events	Warfarin Total	Weight	Risk Ratio M-H, Random, 95% CI
Bassiouny 2013	1	376	1	623	23.7%	1.66 [0.10, 26.41]
Bernard 2013	0	155	0	44		Not estimable
Haines 2012	2	222	0	222	19.8%	5.00 [0.24, 103.56]
Ichiki 2012	0	30	0	180		Not estimable
Kaseno 2012	0	110	0	101		Not estimable
Kim 2012	0	191	0	572		Not estimable
Lakkireddy 2012	3	145	0	145	20.8%	7.00 [0.36, 134.32]
Maddox 2013	1	212	0	251	17.8%	3.55 [0.15, 86.67]
Mendoza 2012	0	60	1	58	0.0%	0.32 [0.01, 7.76]
Nin 2012	0	45	1	45	18.0%	0.33 [0.01, 7.97]
Pavaci 2012	1	27	0	27	0.0%	3.00 [0.13, 70.53]
Rowley 2012	2	113	2	169	0.0%	1.50 [0.21, 10.46]
Snipelsky 2012	0	31	0	125		Not estimable
Yamaji 2012	0	106	0	397		Not estimable
Total (95% CI)		1328		2380	100.0%	2.39 [0.62, 9.18]
Total events	7		2			

Heterogeneity: Tau² = 0.00; Chi² = 2.35, df = 4 (P = 0.67); I² = 0%
Test for overall effect: Z = 1.26 (P = 0.21)

Favours dabigatran / Favours warfarin

Major Bleeding

Study or Subgroup	Dabigatran Events	Dabigatran Total	Warfarin Events	Warfarin Total	Weight	Risk Ratio M-H, Random, 95% CI
Bassiouny 2013	4	376	8	623	27.5%	0.83 [0.25, 2.73]
Bernard 2013	2	155	2	44	0.0%	0.28 [0.04, 1.96]
Haines 2012	3	222	3	222	17.0%	1.00 [0.20, 4.90]
Ichiki 2012	4	30	4	180	0.0%	6.00 [1.59, 22.71]
Kaseno 2012	0	110	2	101	0.0%	0.18 [0.01, 3.78]
Kim 2012	4	191	12	572	30.4%	1.00 [0.33, 3.06]
Lakkireddy 2012	9	145	1	145	10.7%	9.00 [1.16, 70.13]
Maddox 2013	1	212	3	251	9.0%	0.39 [0.04, 3.77]
Mendoza 2012	0	60	0	58		Not estimable
Nin 2012	0	45	0	45		Not estimable
Pavaci 2012	0	27	0	27		Not estimable
Rowley 2012	0	113	1	169	0.0%	0.50 [0.02, 12.09]
Snipelsky 2012	0	31	0	125		Not estimable
Yamaji 2012	0	106	4	397	5.5%	0.41 [0.02, 7.62]
Total (95% CI)		1328		2380	100.0%	1.05 [0.52, 2.12]
Total events	21		31			

Heterogeneity: Tau² = 0.09; Chi² = 5.68, df = 5 (P = 0.34); I² = 12%
Test for overall effect: Z = 0.14 (P = 0.89)

Favours dabigatran / Favours warfarin

Minor Bleeding

Study or Subgroup	Dabigatran Events	Dabigatran Total	Warfarin Events	Warfarin Total	Weight	Risk Ratio M-H, Random, 95% CI
Bassiouny 2013	7	376	16	623	15.4%	0.72 [0.30, 1.75]
Bernard 2013	1	155	2	44	0.0%	0.14 [0.01, 1.53]
Haines 2012	4	222	2	222	4.2%	2.00 [0.37, 10.81]
Kaseno 2012	5	110	11	101	0.0%	0.42 [0.15, 1.16]
Kim 2012	5	191	19	572	12.6%	0.79 [0.30, 2.08]
Lakkireddy 2012	12	145	8	145	15.9%	1.50 [0.63, 3.56]
Maddox 2013	1	212	2	251	2.1%	0.59 [0.05, 6.48]
Mendoza 2012	1	60	1	58	0.0%	0.97 [0.06, 15.09]
Nin 2012	9	45	20	45	26.6%	0.45 [0.23, 0.88]
Pavaci 2012	2	27	4	27	0.0%	0.50 [0.10, 2.50]
Rowley 2012	5	113	33	169	0.0%	0.23 [0.09, 0.56]
Snipelsky 2012	6	31	21	125	17.8%	1.15 [0.51, 2.61]
Yamaji 2012	2	106	11	397	5.4%	0.68 [0.15, 3.03]
Total (95% CI)		1328		2380	100.0%	0.82 [0.58, 1.15]
Total events	46		99			

Heterogeneity: Tau² = 0.00; Chi² = 6.92, df = 7 (P = 0.44); I² = 0%
Test for overall effect: Z = 1.16 (P = 0.25)
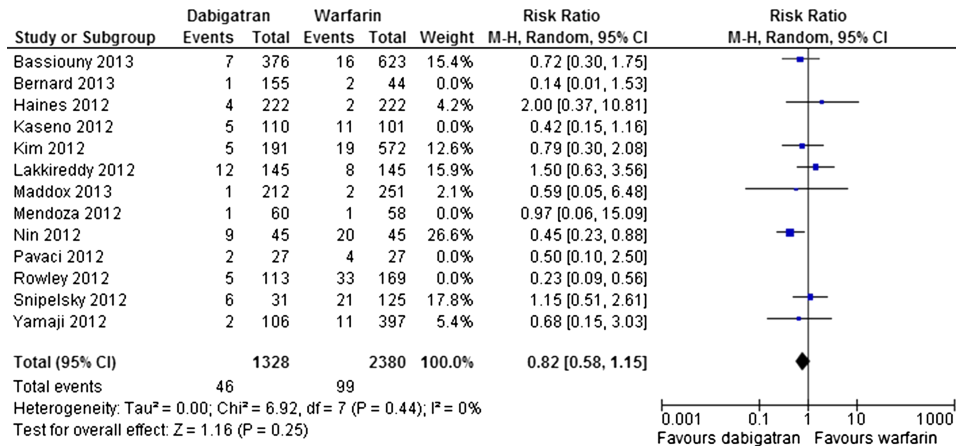
Favours dabigatran / Favours warfarin

Figure 7 Forest plot illustrating the sensitivity analysis restricting data to higher quality full text articles (Delphi criteria or Newcastle–Ottawa Scale ≥5). M-H, Mantel–Haenszel.

CONCLUSIONS

The rate of thromboembolic complications and/or major bleeding in patients on dabigatran undergoing AF catheter ablation is low and similar to that seen with warfarin.

These results may suggest the feasibility and safety of AF catheter ablation in patients regularly treated with dabigatran. However, further prospective and randomised studies are still necessary to confirm these findings and clarify which periprocedural regimen can minimise the risk of thromboembolic complications with dabigatran.

manuscript. RP, JPA, SC, AB, BC, NC, KN, EM and SB carefully and critically revised this version and suggested the necessary changes for its improvement. The final version of the manuscript was revised by RP, JPA, SC, AB, BC, NC, KN, EM and SB and a group discussion was conducted with all authors before the final approval of the manuscript.

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