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Efficacy and safety of rivaroxaban compared with vitamin K antagonists for peri-procedural anticoagulation in catheter ablation of atrial fibrillation: a systematic review and meta-analysis

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Rivaroxaban is increasingly used in patients undergoing catheter ablation of atrial fibrillation (AF). In the absence of large controlled trials, a comprehensive meta-analysis of the literature appears to be the best way to obtain reliable evidence on rare peri-procedural outcomes such as thromboembolic or bleeding events. We aimed to provide a detailed analysis of currently available data on safety and efficacy of peri-procedural rivaroxaban in patients undergoing AF ablation. We performed a systematic search of the English language literature for studies comparing peri-procedural rivaroxaban therapy with vitamin K antagonists (VKAs) and reporting detailed data on bleeding and/or thromboembolic complications. The Peto odds ratio (POR) was used to pool data into a fixed-effect meta-analysis. A total of 7400 patients undergoing catheter ablation were included in 15 observational and 1 randomized studies of which 1994 were receiving rivaroxaban and 5406 VKA. The risk of thromboembolism trended to be lower in the rivaroxaban group [4/1954 vs. 19/5219, POR 0.40, 95% confidence interval (CI), 0.16–1.01, $P = 0.052$]. Major bleeding events occurred in 23 of 1994 cases (1.15%) in the rivaroxaban and 90 of 5406 (1.66%) in the VKA group (POR 0.74, 95% CI, 0.46–1.21, $P = 0.23$). A total of 87 minor bleeding events were reported in 1753 patients (4.96%) in the rivaroxaban group and in 165 of 4009 patients (4.12%) in the VKA group (POR 0.84, 95% CI 0.63-1.11, $p = 0.22$). In patients undergoing AF ablation, rivaroxaban appears to be an effective and safe alternative to VKA.

Keywords Rivaroxaban • Catheter ablation • Atrial fibrillation • Peri-procedural anticoagulation • Stroke • Oral anticoagulation

Introduction

Catheter ablation has evolved as the standard of care in selected patients with symptomatic atrial fibrillation (AF).[1,2] Catheter ablation carries a notable risk for peri-procedural thromboembolic and bleeding events. A worldwide survey on peri-procedural complications revealed that 4.5% of patients experienced a major complication (major bleeding 2.8%, thromboembolic event 0.94%).[3] According to the results of observational and randomized trials, uninterrupted warfarin therapy seems to be superior over bridging with unfractionated (UFH) or low-molecular-weight heparin (LMWH).[4,5] However, vitamin K antagonist (VKA) therapy has known limitations such as a narrow therapeutic window, need for frequent dose adjustments based on repeated INR measurements, a long onset and offset time, many drug–drug interactions, to name the most important ones.[6–8]

Novel oral anticoagulants (NOACs) have handling advantages over VKAs, including a fast onset of action, lack of requirement for routine coagulation monitoring, and fewer drug–drug interactions, thus simplifying anticoagulation management substantially.

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What's new?

- Catheter ablation of atrial fibrillation (AF) is an established treatment modality but carries a distinct risk of thromboembolism. Hence, anticoagulation before, during, and after the procedure is mandatory. This systematic review and comprehensive meta-analysis of the current literature indicates that rivaroxaban appears to be an effective and safe alternative to vitamin K antagonists in patients undergoing catheter ablation of AF. It may offer advantages in terms of handling anticoagulation in this clinical scenario.

Moreover, large-scale randomized trials in the general AF population demonstrated non-inferior efficacy and safety of NOACs over warfarin.[9–11]

In the setting of catheter ablation of AF, some small observational studies[12–26] and one randomized trial[27] indicated a similar safety and efficacy profile of rivaroxaban compared with warfarin. However, most of these studies comprised only small patient samples and were hence statistically underpowered for rare outcomes, i.e. thromboembolism or major bleeding. Accordingly, the present meta-analysis of all respective studies aims to provide comprehensive data on rivaroxaban in the setting of AF ablation.

Methods

Study selection

This systematic review was performed according to the PRISMA Statement for reporting systematic reviews and meta-analyses.[28] Our predefined review protocol was published in the PROSPERO database under the registration number of CRD42015017085.[29]

A comprehensive search was conducted in MEDLINE, COCHRANE Library, and 'Web' databases from January 2010 through April 2015 focusing on full-sized papers published in the English language reporting data on the safety and efficacy of peri-procedural rivaroxaban in patients undergoing AF ablation. Abstracts were included when critically relevant. Studies eligible for inclusion were identified by using the following terms with all variations in spelling: 'catheter ablation', 'rivaroxaban', and 'mouth/oral anticoagulants'. Additional publications were identified using the reference lists of selected manuscripts. Three reviewers independently evaluated all potentially relevant articles for eligibility.

The eligibility criteria for this meta-analysis were as follows:

(1) inclusion of patients undergoing catheter ablation of AF,
(2) reported peri-procedural bleeding and/or thromboembolic complications related to the use of interrupted or uninterrupted rivaroxaban therapy,
(3) investigated outcomes with an interrupted or uninterrupted VKA comparator arm.

Any disagreement was subsequently resolved by consensus. Studies reporting only composite patients groups, but no specific data on catheter ablation or investigated outcomes without a VKA comparator arm were excluded.

Baseline characteristics, study design, percentage of paroxysmal AF, details on peri-procedural anticoagulation (i.e. timing of the first-held and restarting dose of anticoagulants, possibly LMWH/heparin bridging), efficacy and safety outcomes were extracted from included studies independently by two investigators. Corresponding authors were contacted for unpublished information and permission in case of missing relevant data sets.

Endpoints of interest

The efficacy outcome was defined as a composite endpoint of symptomatic thromboembolic events including ischaemic stroke, transient ischaemic attack (TIA), or systemic thromboembolism. Major bleeding constituted the primary safety outcome. The definition of bleeding was mainly based on the criteria of the International Society of Thrombosis and Hemostasis.[30] In general, major bleeding was defined as fatal bleeding, bleeding that was symptomatic and occurred in a critical area or organ, bleeding causing a drop in haemoglobin level of 2 g/dL or more, severe enough to require $\geq$2 units of blood, or a specific therapeutic intervention, or cessation of anticoagulation for $>$7 days. Pericardial effusions were considered as major bleeding events if it not specified otherwise. Minor bleeding consisted of any clinically noted bleeding not meeting criteria for major haemorrhage.

Statistical analysis

Methodological quality of all studies was assessed using the Methodological Index for Non-Randomized Studies (MINORS).[31] The Peto odds ratio (POR) with 95% confidence intervals (CIs) was used to pool data into a fixed-effect meta-analysis given the low event rates for the overall effect in this meta-analysis.[32,33] A Forest plot was constructed of individual trials with the pooled estimates. Heterogeneity between individual trial estimates was assessed using the Q statistic and I^2 statistic. For I^2, a value of $>$50% was considered to indicate significant heterogeneity.[34] Publication bias was assessed using the funnel plot, the trim and fill method of Duval and Tweedie,[35] and an adjusted rank correlation test according to Begg and Mazumdar.[36] Sensitivity analyses regarding uninterrupted VKA or rivaroxaban therapy, use of LMWH/heparin bridging, and holding $\leq$2 dose or holding $>$2 doses of rivaroxaban were performed. All statistical analyses were conducted utilizing Comprehensive Meta-Analysis 3.3 (Biostat, Inc., USA).

Results

Study characteristics

As shown in *Figure 1*, a total of 16 studies were selected for the present analysis. These studies fulfilling our predefined selection criteria involved 7400 patients of which 1994 subjects received rivaroxaban. Of all identified studies, only one[27] was a randomized controlled clinical trial, whereas the remainders were observational retrospective[12,13,16,18–26] or prospective[14,15,17] studies. The vast majority were single-centre observational studies, with the exception of three multicentre studies[14,23,27] and one based on a national registry.[17] Seven included reports were assessed to be high-quality publications (average MINORS score 16.2 $\pm$ 3.3). *Table 1* provides details of all included studies.

The majority of the studies used rivaroxaban 15 or 20 mg OD. Two reports from Japan used 10 or 15 mg rivaroxaban OD.[19,20] Ten studies[13,14,16,18,19,23–27] used an uninterrupted VKA strategy. Most of the studies discontinued rivaroxaban 24–48 h prior to the procedure (i.e. typically held 1 or 2 doses) with or without LMWH/heparin bridging (*Table 1*). Rivaroxaban was generally resumed within 12 h after the procedure. Only 6 studies out of 15[14,18,19,23,24,27] assessed the efficacy and safety of an uninterrupted rivaroxaban regimen. The target activated clotting time (ACT) during ablation was between 300 and 400 s in most studies.

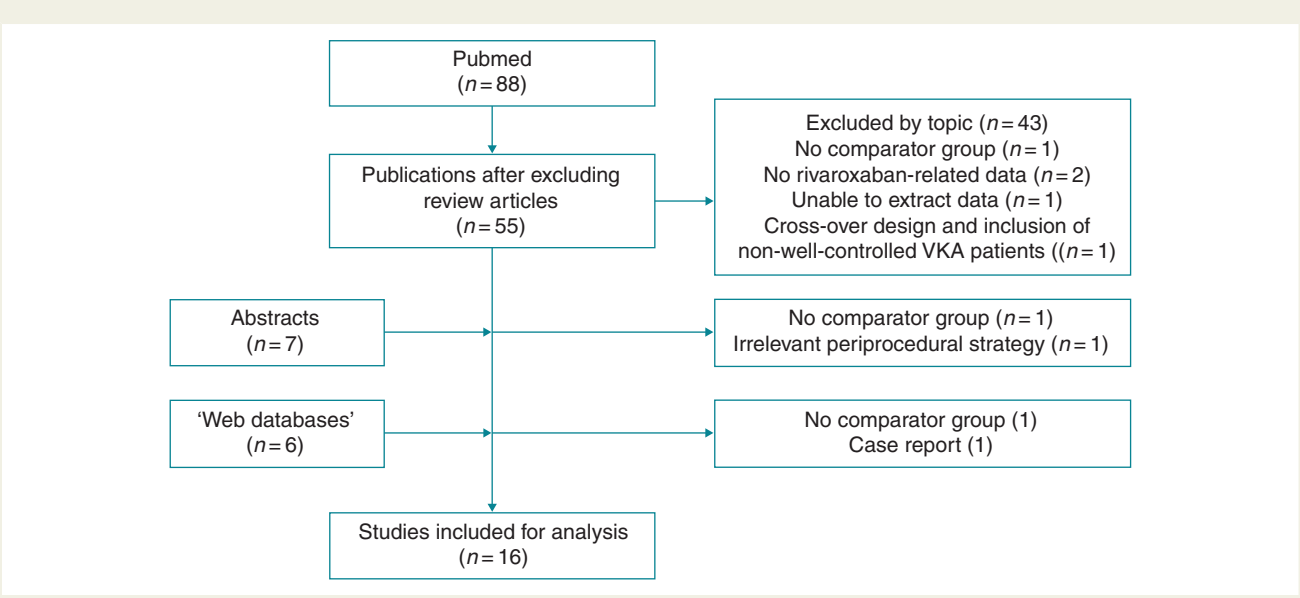

Figure 1 Flow chart describing systematic literature search and selection process.

Efficacy and safety outcome events

A total of 23 thromboembolic events were observed in 15 studies. One study did not report data on efficacy.[25] Fewer thromboembolic events were reported in rivaroxaban-treated patients compared with those receiving VKA (4/1954 vs. 19/5219; POR 0.40, 95% CI 0.16–1.01, $P = 0.052$; $I^2 = 0\%$) (*Figure 2*).

Major bleeding events were reported for all of the studies and were observed in 1.15% of rivaroxaban (23/1994) and 1.66% of VKA patients (90/5406) (POR 0.74, 95% CI 0.46–1.21, $P = 0.23$; $I^2 = 0\%$) (*Figure 3*). The overall rate of severe pericardial effusion/tamponade was 0.88% (65/7400).

Data for minor bleeding were available in 14 of 16 studies. Minor bleeding events were reported at a pooled rate of 4.96% (87/1753) in rivaroxaban-treated patients compared with 4.12% in VKA-treated patients (165/4009) (POR 0.84, 95% CI 0.63–1.11, $P = 0.22$; $I^2 = 0\%$) (*Figure 4*).

Only two fatal complications (one ruptured cerebral aneurysm on rivaroxaban and one vascular death on VKA) were reported.[21,27]

A consistent value of 0% of the I^2 along all three outcome measures indicated lack of relevant statistical heterogeneity. The sensitivity analyses described in the method section revealed no significant differences compared with the main results (Supplementary material online, *Table S1–3*). There was a trend towards better performance of uninterrupted rivaroxaban as compared with interrupted (>2 doses held) for both, major and minor bleeding events (*Figure 5*).

Publication bias

According to the rank correlation test of Begg and Mazumdar, there was no evidence of significant publication bias (thromboembolism: $\tau = -0.036$, $P = 0.44$; major bleeding: $\tau = -0.105$, $P = 0.29$; minor bleeding: $\tau = -0.013$, $P = 0.48$). Furthermore, corresponding to the Duval and Tweedie's trim and fill input method, there was no evidence that publication bias would impact on the overall effect size observed (thromboembolism POR: 0.401 vs. 0.553; major bleeding POR: 0.743 vs. 0.789; minor bleeding POR: 0.834 vs. 0.834) (funnel plots with the imputed studies in Supplementary material online, *Figures S1–3*).

Discussion

Main findings

The present meta-analysis of 15 observational studies[12–26] and 1 recently published randomized trial[27] comprising 7400 patients undergoing AF ablation demonstrates similar efficacy and safety of rivaroxaban when compared with VKA in preventing thromboembolic and bleeding events during AF ablation.

Thromboembolic events during atrial fibrillation ablation

Catheter ablation has matured as an established treatment modality in patients with symptomatic AF. This procedure carries the risk of local and systemic complications, with stroke occurring at an incidence of 0.5–1.0%.[3] Atrial fibrillation ablation also carries a risk for silent cerebrovascular events, the consequences of which remain unclear.[37,38] The increased thromboembolic risk during AF ablation seems to be related to the underlying prothrombotic state associated with the arrhythmia and to specific ablation-related factors, such as placement of multiple venous sheaths, trans-septal punctures, activation of the clotting cascade via application of radiofrequency energy, and atrial stunning.[39]

Hence, there is a clear need to protect patients from thromboembolic events during AF ablation, but there is still no consensus regarding the optimal anticoagulation regimen. Current guidelines therefore recommend the use of uninterrupted warfarin,[1,2,40] mainly based on results of a randomized clinical trial demonstrating

Table 1 Publications included in meta-analysis

Study	Design	Subjects total	Subjects rivaroxaban	Follow-up	Paroxysmal AF (%)	VKA type and dosing	Rivaroxaban dosing	Quality (MINORS score)
Bernard[12]	Single-centre study	119	75	30 days	R 57, VKA 50	Warfarin, discontinued within 24 h prior to the procedure and restarted within 24 h after the procedure	Discontinued within 24 h prior to the procedure and restarted within 24 h after the procedure	15
Gadiyaram[13]	Single-centre study	338	54	n.a.	n.a.	Warfarin uninterrupted/ interrupted with LMWH bridging	Discontinued within 48 h prior to the procedure with LMWH bridging and restarted within 24 h after the procedure	13
Lakkireddy[14]	Multicentre, prospective, observational study	642	321	30 days	R 51, VKA 51	Warfarin, uninterrupted	Uninterrupted	20
Providencia[15]	Single-centre, prospective, observational study	380	188	30 days	R 63, VKA 53	Fluidione/warfarin/ acenocoumarol, interrupted with heparin/LMWH bridging	Discontinued within 24–48 h prior to the procedure	20.5
Stepanyan[16]	Retrospective analysis	212	98	≥30 days	71	Warfarin, uninterrupted	Discontinued within 36 h prior to the procedure with heparin bridging	17.5
Murakawa[17]	National registry	1845	37	n.a.	64	Warfarin, interrupted	Typically discontinued >24 h prior to the procedure	12
Mendoza[18]	Single-centre study	138	80	30 days	R 67, VKA 43	Warfarin, uninterrupted	Uninterrupted	15
Tao[19]	Single-centre study	140	70	n.a.	72.9	Warfarin, uninterrupted	Uninterrupted	14
Toyama[20]	Single-centre study	281	50	n.a.	n.a.	Warfarin, interrupted	Discontinued within 24 h prior to the procedure and restarted at 2 h after the procedure	13
Winkle[21]	Single-centre retrospective study	1300	187 (pre-ablation)	n.a.	R 27, VKA 22	Warfarin, interrupted	Discontinued within 36 h prior to the procedure without LMWH bridging and restarted within 24 h after the procedure	14.5
Kochhauser[22]	Single-centre retrospective study	460	141	11–18 months	69–75	Warfarin, interrupted with LMWH bridging	Last dose in the morning of the day before the procedure and resumed 8 h post-sheath removal	17
Di Biase[23]	Multicentre study	392	196	n.a.	0	Warfarin, uninterrupted	Uninterrupted	15
Dillier[24]	Single-centre non-randomized study	544	272	n.a.	R 49, VKA 46	Phenprocoumon, uninterrupted	Uninterrupted	18.5
Snipelisky[25]	Single-centre retrospective study	127	40	n.a.	n.a.	Warfarin, uninterrupted	Discontinued within 12 h prior to the procedure	13.5
Armbruster[26]	Retrospective cohort study	234	61	n.a.	n.a.	Warfarin, uninterrupted	By most patients discontinued >24 h and restarted within 12 h after the procedure	17
Cappato[27]	Multicentre randomized controlled trial	248	124	30 ± 5 days	73.4	Warfarin, uninterrupted	Uninterrupted	24

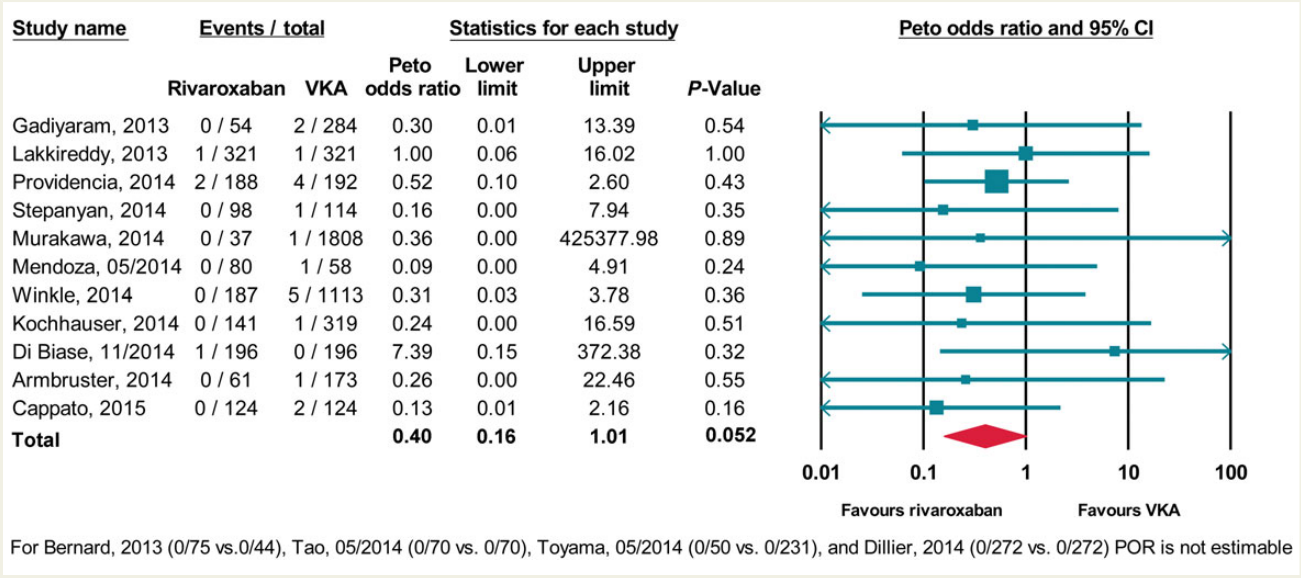

Figure 2 Forest plot of thromboembolic events.

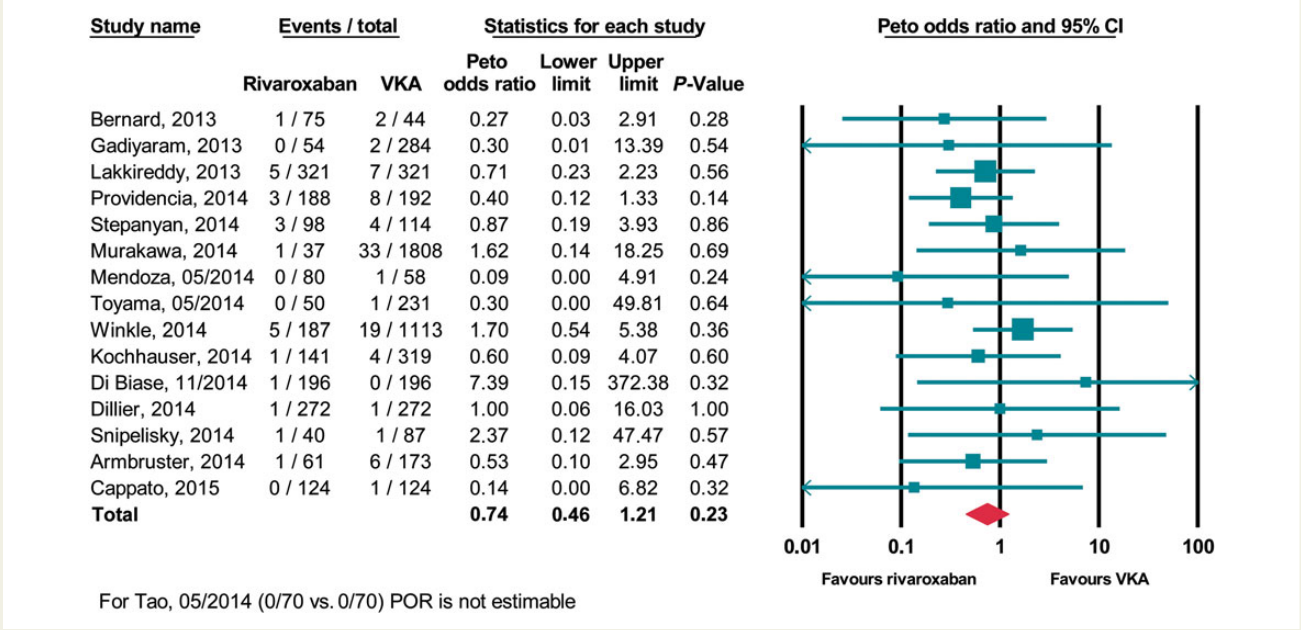

Figure 3 Forest plot of major bleeding events.

superior efficacy and safety of uninterrupted VKA therapy vs. bridging.[5]

However, limitations of and difficulties in using VKA therapy are well known.[6–8] Given the non-inferior efficacy and safety of NOACs in general stroke prevention in AF,[9–11] it seems logical to evaluate these new compounds also in the setting of AF ablation. The first observational studies in patients undergoing AF ablation used dabigatran. A meta-analysis of 10 such studies comprising 3648 patients showed similar efficacy of this compound compared with warfarin when given during AF ablation.[41]

For rivaroxaban, several observational studies reported similar findings.[12–26] In addition, the first prospective randomized study of a NOAC in 228 ablation patients randomized to rivaroxaban or VKA was recently published.[27] The present comprehensive meta-analysis of all rivaroxaban studies in the setting of AF ablation confirms the efficacy of this NOAC in preventing cerebrovascular events during AF ablation. Only 23 strokes/TIA were reported in almost 7400 patients (overall incidence 0.32%). This overall event rate was lower than previously reported,[3] perhaps due to increasing experience of centres performing AF ablations, improved ablation

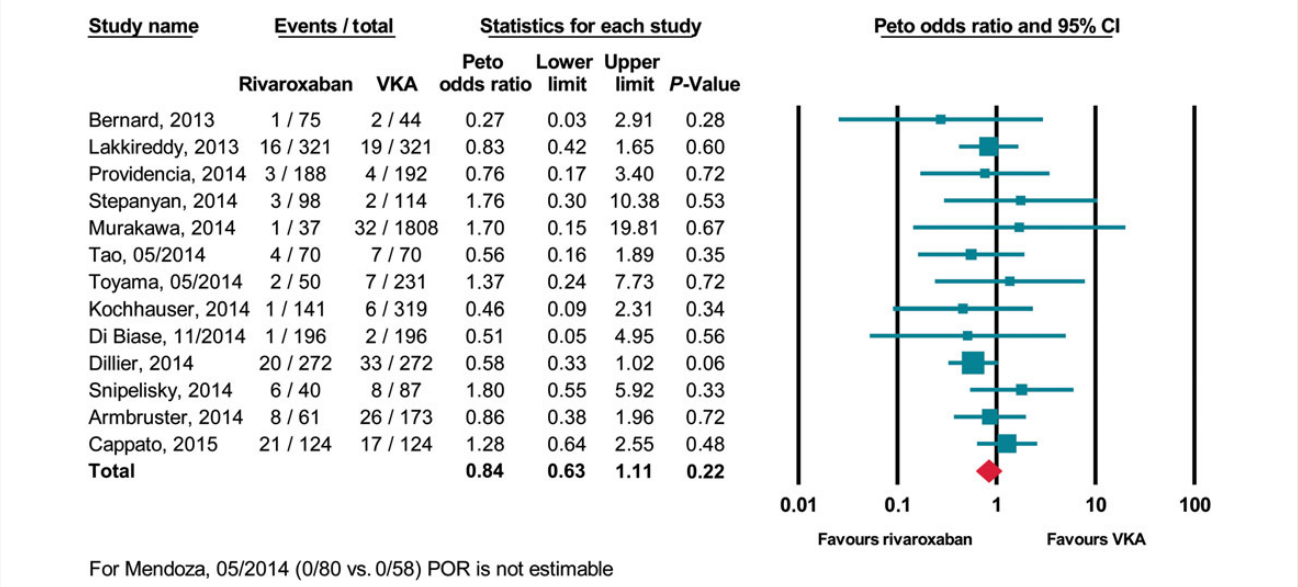

Figure 4 Forest plot of minor bleeding events.

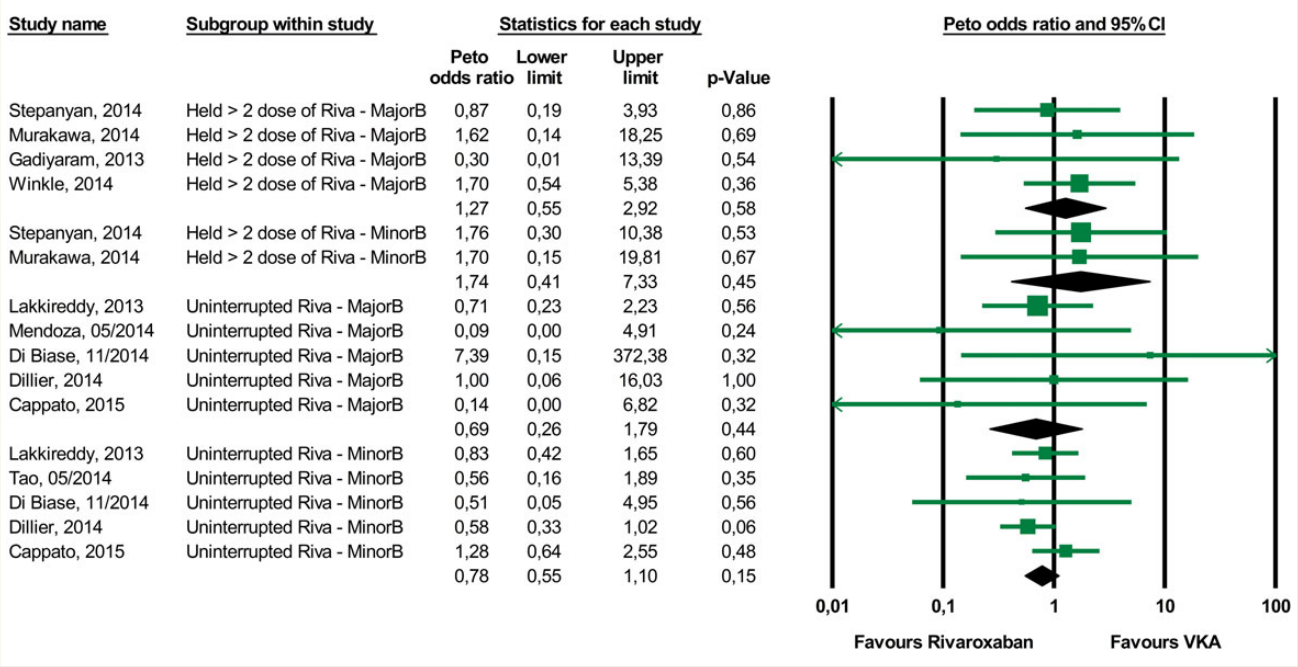

Figure 5 Bleeding risk in studies using uninterrupted rivaroxaban or holding >2 dose of rivaroxaban.

techniques, or due to underreporting in these mostly observational studies. Despite the small numbers, there was a trend towards less cerebrovascular events with rivaroxaban than with VKA. Our study extends the findings of previous meta-analyses[42–45] by including data from 7400 patients from 15 retrospective and 1 prospective randomized studies.

Risk of bleeding during atrial fibrillation ablation

Previous reports indicate an incidence of 2.8% of major bleeding events in patients undergoing AF ablation.[3] Novel oral anticoagulants have in general been demonstrated to have similar or even lower bleeding rates than VKA.[9–11] The present meta-analysis

of rivaroxaban studies shows similarly low bleeding incidences with this NOAC compared with VKA, in line with the observations from the randomized rivaroxaban study for which all bleeding episodes were centrally adjudicated.[27] It is also in agreement with recent findings using apixaban for peri-procedural anticoagulation in AF ablation.[46]

Unresolved issues in the use of novel oral anticoagulants during atrial fibrillation ablation

All NOACs have significant handling advantages over VKA in general and in the setting of AF ablation. Current expert consensus documents recommend temporary interruption of NOAC therapy prior to elective procedures including AF ablation.[47] The studies analysed here were not uniformly designed in this respect; whereas some used continuous rivaroxaban administration,[14,18,19,23,24,27] others stopped NOAC administration for one or more doses,[12,13,15–17,20–22,25,26] as in a recent publication on this topic.[48]

Limitations

This meta-analysis is subject to all potential limitations of this kind of analysis. We did not have access to individual patient data from all studies reviewed but had to rely on published information. The vast majority of the data stem from retrospective observational studies, and hence potential confounding cannot be excluded. Patient populations enrolled in individual trials were heterogeneous with regard to the use of the anticoagulants (i.e. uninterrupted/interrupted VKA or rivaroxaban therapy, use of LMWH/heparin bridging, the number of hold dose of rivaroxaban). However, our sensitivity analyses of various patient subgroups revealed no significant differences compared with the main results (Supplementary material online, *Table S1–3*). There were large variations in the follow-up period of patients, and no long-term follow-up data were available in some of the studies. Furthermore, we had no detailed data available to evaluate if major bleeds on rivaroxaban were associated with more requirements for blood products than those occurring on VKA. These limitations emphasize the need for further randomized trials.

Conclusion

According to this comprehensive meta-analysis, rivaroxaban appears to be a safe alternative to warfarin with no apparent difference or no signal of a difference in efficacy.

Supplementary material

Supplementary material is available at *Europace* online.

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