◆META-ANALYSIS ◆

Impact of Long-Term Warfarin Treatment on EVAR Durability: A Meta-Analysis

Miltos K. Lazarides, MD, FEBVS; George S. Georgiadis, MD; Dimitrios G. Charalampidis, MD; George A. Antoniou, MD, PhD; Efstratios I. Georgakarakos, MD; and George Trellopoulos, MD

Department of Vascular Surgery, Democritus University Hospital, Alexandroupolis Greece.

Purpose: To evaluate whether postoperative long-term oral anticoagulation affects the durability of endovascular aneurysm repair (EVAR) and whether it is associated with an increased incidence of endoleak and subsequent need for reintervention.
Methods: A literature search was performed to identify studies of abdominal aortic aneurysm patients undergoing EVAR including an arm receiving warfarin postoperatively and reporting the frequency of any endoleaks and/or persistent type II endoleaks and reinterventions. The search identified 81 articles, of which 5 observational cohort studies ultimately met the inclusion criteria.
Results: Postoperative anticoagulation was required in 219 (14.6%) of the 1499 patients in the selected studies. The pooled effects analysis found that EVAR patients receiving long-term warfarin postoperatively had significantly more endoleaks of any type (OR 1.77, 95% CI 1.26 to 2.48, $p=0.001$) as well as persistent type II endoleaks (OR 1.58, 95% CI 1.05 to 2.37, $p=0.03$) compared with patients not on anticoagulation; however, there was no statistically significant difference in the reintervention rate between the groups.
Conclusion: Long-term anticoagulation in EVAR patients was associated with a statistically significant increase in any endoleak and persisting type II endoleaks, although it was not linked to an increased risk of reintervention. Close monitoring for EVAR patients who require long-term oral anticoagulation is advised.

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Key words: abdominal aortic aneurysm, endovascular aneurysm repair, endoleak, persistent type II endoleak, warfarin, anticoagulants, reintervention, meta-analysis, systematic review

Endovascular aneurysm repair (EVAR) is currently the treatment of choice for most uncomplicated infrarenal abdominal aortic aneurysms (AAA). As AAA is an age-related disease, more elderly patients will be referred for AAA repair and some of them will need long-term anticoagulation postoperatively for various comorbidities, notably atrial fibrillation. However, very little information is available on the effect of long-term oral anticoagulation on EVAR durability. There is no general agreement about the role of oral anticoagulants on endoleak persistence following EVAR, with the few existing studies reporting conflicting results.[1–5] A systematic review and meta-analysis was conducted to evaluate whether long-term anticoagulation affects EVAR durability and whether it is associated with an increased incidence of endoleak and subsequent need for reintervention.

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Corresponding author: Miltos K. Lazarides, MD, Marathonos 13 (N Chili), 68100 Alexandroupolis, Greece. E-mail: *mlazarid@med.duth.gr*

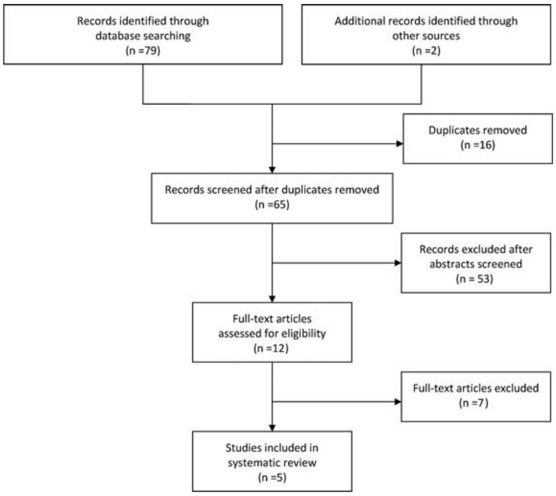

Figure 1 ◆ Flowchart of systematic review in accordance with PRISMA guidelines

METHODS

A systematic literature search confined to studies published in English was performed via MEDLINE/PubMed, SCOPUS, and web search engines using the following keywords with Boolean operators: "endoleak" OR "endotension" AND "warfarin" OR "anticoagulants" OR "Coumadin." References in retrieved articles were manually searched for additional material.

Studies were eligible for inclusion provided they fulfilled the following criteria: (1) reported on a cohort of AAA patients undergoing EVAR, including patients using long-term oral anticoagulants postoperatively and patients not on anticoagulants, and (2) reported the frequency of any endoleaks and/or persistent type II endoleaks and any ruptures/reinterventions for both groups separately. It is obvious that no randomized trials could be found, as no patient can be assigned to anticoagulation treatment with no indication and vice versa.

The search identified 81 articles (Fig. 1), of which 5 observational single institution cohort studies[1–5] met the inclusion criteria and were included in the review. Seven full text articles were excluded from the analysis: 3 were case reports on persistent endoleak or sac enlargement in patients receiving long-term oral anticoagulation,[6–8] one article did not give the number of patients on anticoagulants,[9] and 3 articles included only patients with type II endoleaks, some on anticoagulants, with no inclusion of patients without endoleaks.[10–12]

Data were extracted from the studies and entered into a computer file. Endoleak occurrences and reinterventions were recorded as adverse events. The probability of an adverse event occurring in one group or the other was presented as the odds ratio (OR), where an OR <1 indicated a lower endoleak rate in the warfarin group and an OR >1 indicated a lower rate of endoleaks in the non-warfarin group.

The pooled results [OR and 95% confidence intervals (CI)] for all combined studies were calculated and displayed using a fixed-effects model when there was no evidence of significant between-study heterogeneity; otherwise, a random-effects model was used. Heterogeneity was assessed using the I^2 index, which is appropriate for evaluating variances in a small number of studies. I^2 values $<25\%$ indicate low heterogeneity, while I^2 values $>50\%$ significant heterogeneity.[13] Sensitivity analysis to assess the influence of individual studies on the overall outcome was not performed due to the small number of included articles.

The Newcastle-Ottawa Scale (NOS) was used to assess the quality of the non-randomized studies in this meta-analysis.[14] This scale was developed to assess the quality of studies using a star system (maximum 9 stars) in which a study was judged on three broad perspectives: the selection of the study groups; the comparability of the groups; and the ascertainment of the outcome of interest. Studies achieving $\geq$6 stars were considered to be of higher quality.

This meta-analysis was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[15] Statistical analysis was performed using the free RevMan 5.2 software (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark; 2012).

RESULTS

Postoperative anticoagulation was required in 219 (14.6%) of the 1499 patients included in this analysis. All 5 studies reported outcomes

TABLE
Characteristics of Studies Included in the Analysis

	Study Design	Mean Follow-up, mo	INR	Primary (P) and Secondary (S) Endpoints	NOS
Fairman 2002[1]	Retrospective	18	>2	P: endoleak	6
Biebl 2005[2]	Retrospective	16.3	2–3	P: death, rupture S: reintervention, endoleak, sac enlargement	5
Abularrage 2010[4]	Retrospective	34.8	NR	P: persistent type II endoleaks	8
Bobadilla 2010[3]	Prospective	25	2–3	P: endoleak, sac expansion, reintervention	6
Johnson 2013[5]	Retrospective	29	NR	P: death, rupture, reintervention S: endoleak, sac enlargement	5

INR: International Normalized Ratio, NOS: Newcastle-Ottawa Scale, NR: not reported.

on all endoleaks and 4 on persistent (≥1 month) type II endoleaks (Table). Of the 1499 patients who underwent EVAR, 288 had an endoleak of any type, while persistent type II endoleak was present in 217 of the 1136 patients for whom this variable was reported.

Since there was no significant heterogeneity among the included studies (Fig. 2), the fixed-effects model was used. The pooled effects analysis found that EVAR patients receiving long-term warfarin postoperatively had significantly more endoleaks of any type (OR 1.77, 95% CI 1.26 to 2.48, $p=0.001$; Fig. 2A) as well as persistent type II endoleaks (OR 1.58, 95% CI 1.05 to 2.37, $p=0.03$; Fig. 2B) compared with patients not on anticoagulation.

Only 3 studies reported on reintervention rates (Fig. 2C), in the vast majority characterized as endoleak-specific; however, there was no statistically significant difference between the two groups (OR 2.14, 95% CI 0.60 to 7.62, $p=0.24$; $I^2=74\%$, random-effect model). In the same 3 studies, the number of late ruptures was also reported; however, the small number (3 ruptures in total, all in the non-warfarin group) did not permit any further statistical analysis. Visual inspection of the funnel plots did not suggest publication bias, but interpretation was limited by the small number of studies.

DISCUSSION

As the population of EVAR patients grows, it is likely that long-term oral anticoagulation will become more prevalent; indeed, the 15% rate of patients in this review on warfarin would tend to support that view. Although the antiplatelet monotherapy commonly prescribed in EVAR patients has been demonstrated to have no significant impact on outcomes,[16] this is not the case for oral anticoagulants. Theoretically, full anticoagulation with an International Normalized Ratio (INR) >2 would impair the thrombotic process within the excluded aneurysm sac, predisposing to early and late endoleaks and resulting in a less durable repair. However, current literature on this topic presents conflicting results.[1–5] In the first study of this subject, Fairman et al.[1] initially observed no association between anticoagulants and early or late endoleaks. However, they found significantly decreased rates of aneurysm sac shrinkage in patients treated with warfarin, and they hypothesized that this phenomenon may be due to a delayed thrombosis of the excluded aneurysm. Similarly, Biebl et al.[2] found anticoagulation safe following EVAR; it was not associated with mortality, risk for rupture, or reintervention rate, but they noticed a trend toward more early endoleaks in the warfarin group. In contradiction, Bobadilla et al.[3] related warfarin therapy with significantly increased endoleak occurrence, specifically type II endoleaks. This finding was also associated with persistent sac expansion but not increased rupture rate, and the authors advised close monitoring for such patients. Abularrage et al.[4] reported 15% prevalence of persistent type II endoleaks in patients on

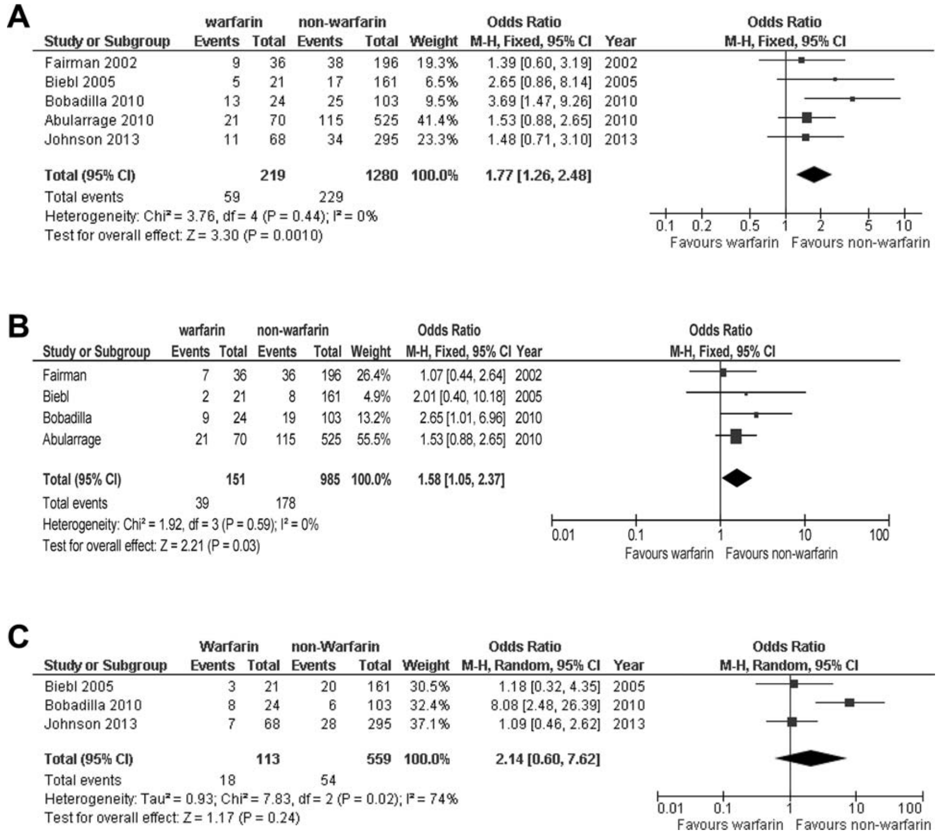

Figure 2 ◆ Pooled estimates of (**A**) any endoleak, (**B**) persisting ($\geq$1 month) type II endoleak, and (**C**) reinterventions following EVAR in patients using oral anticoagulants (warfarin) vs. patients not on warfarin. Odds ratios are shown with 95% confidence intervals (CI).

warfarin in comparison with 11% in those not on anticoagulants. Recently, however, Johnson et al.[5] reported no association of warfarin treatment with statistically significant endoleak occurrence in a large study (n=401).

This meta-analysis demonstrated a statistically significant increase in endoleaks in EVAR patients on long-term oral anticoagulation. The pooled odds of any endoleak occurring in the warfarin group was almost double (OR 1.77) compared to the non-warfarin group. A similar increase but to a lesser extent was also demonstrated in persistent type II endoleaks in the warfarin group (OR 1.58), but this increase was not linked with a significant increase in reinterventions or late ruptures.

The increased risk of any endoleak in anticoagulated patients likely is driven in part by the increased prevalence of type II endoleaks in this group, but the small number of types I and III endoleaks does not permit a definite conclusion. The relatively benign nature of type II endoleaks and their spontaneous resolution under anticoagulant treatment have been noted[2,17]; however, sporadic cases of late rupture or persistent sac enlargement with or without previous detection of endoleak in EVAR patients on long-term anticoagulants sounds a note of caution.[6–8]

There is controversy as to which subgroups of type II endoleaks are benign or require surveillance and treatment in selected cases, but the answer to this question is beyond the scope of this meta-analysis. The association of anticoagulation with endoleak occurrence is supported by these data and by the observation that late secondary endoleaks may appear after the start of warfarin treatment.[9]

Limitations

The most important limitation of this systematic review was that no randomized trials were included (not appropriate as no patient can be assigned to anticoagulation without indication); therefore, the results are prone to selection bias. Several other factors, mostly anatomical, may have an impact on the incidence of endoleak. While type I and III endoleaks represent technical or device failure, type II endoleaks correspond to the patient's anatomy and could be attributed only in part to increased INR level.

The methodological quality of the studies was average, with 2 studies scoring 5 in the Newcastle-Ottawa Scale. In 2 studies there was also no information regarding the INR in the warfarin group, raising doubts about the compliance with treatment. There were also different diagnostic methods in the detection of endoleaks, with Johnson et al.[5] using duplex ultrasound in the majority of their patients, although a recent meta-analysis suggested that unenhanced duplex ultrasound has poor sensitivity for endoleak detection.[18]

Conclusion

This meta-analysis associated long-term anticoagulation in EVAR patients with higher incidences of any endoleak and persisting type II endoleaks. Although the latter were not linked with increased risk of reintervention or rupture, close monitoring of EVAR patients who require long-term oral anticoagulation is advised.

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