Effect of Apixaban on All-cause Death in Patients with Atrial Fibrillation: A Meta-analysis Based on Imputed Placebo Effect

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ABSTRACT

Purpose: Vitamin K antagonists (VKAs) are the standard of care for stroke prevention in patients with atrial fibrillation (AF); therefore, there is not equipoise when comparing newer oral anticoagulants with placebo in this setting.

Methods: To explore the effect of apixaban on mortality in patients with AF, we performed a meta-analysis of apixaban versus placebo using a putative placebo analysis based on randomized controlled clinical trials that compared warfarin, aspirin, and no antithrombotic control. We used data from 2 prospective randomized controlled trials for our comparison of apixaban versus warfarin (ARISTOTLE) and apixaban versus aspirin (AVERROES). Using meta-analysis approaches, we indirectly compared apixaban with an imputed placebo with respect to the risk of death in patients with AF. We used results from meta-analyses of randomized trials as our reference for the comparison between warfarin and placebo/no treatment, and aspirin and placebo/no treatment.

Results: In these meta-analyses, a lower rate of death was seen both with warfarin (odds ratio [OR] 0.74, 95% confidence interval [CI] 0.57–0.97) and aspirin (OR 0.86, 95% CI 0.69–1.07) versus placebo/no treatment. Using data from ARISTOTLE and AVERROES, apixaban reduced the risk of death by 34% (95% CI 12–50%; p=0.004) and 33% (95% CI 6–52%; p=0.02), respectively, when compared with an imputed placebo. The pooled reduction in all-cause death with apixaban compared with an imputed placebo was 34% (95% CI 18–47%; p=0.0002).

Conclusions: In patients with AF, indirect comparisons suggest that apixaban reduces all-cause death by approximately one-third compared with an imputed placebo.

Keywords: apixaban, aspirin, placebo, mortality, warfarin, atrial fibrillation

INTRODUCTION

Anticoagulation with vitamin K antagonists (VKAs) is highly effective for stroke prevention in patients with atrial fibrillation (AF) and, until recently, was the standard of care [1]. Thus, there is not equipoise when comparing newer oral anticoagulants with placebo in this setting.

Patients with AF are at high risk of death, an outcome more common than stroke [2,3], and strategies to improve survival in this population are needed. When compared with placebo (or control), warfarin is highly effective in reducing stroke in patients with AF; however, the effect of warfarin on mortality is less certain with a reported relative risk reduction of 26% (95% confidence interval [CI] 3–43%) of borderline significance in a meta-analysis of 6 trials including a total of 2900 patients who experienced 110 versus 143 deaths. In similar meta-analyses, antiplatelet therapy, compared with placebo (or control), had a much more modest stroke benefit that was statistically uncertain with no significant effect on mortality. When compared directly with antiplatelet therapy, warfarin did not lead to a clear reduction in death. Subsequently, non-vitamin K antagonist oral anticoagulants (NOACs) were studied in large randomized trials and were at least as effective as warfarin at preventing stroke in patients with AF and generally safer than warfarin, particularly in causing less intracranial hemorrhage (ICH), when compared with warfarin [4-7]. Compared with warfarin, the NOACs also appeared to lead to modest reductions in mortality but with borderline statistical significance when individual trial results were analyzed [4-7]. However, a meta-analysis with pooled data from the 4 clinical trials that tested NOACs versus warfarin for patients with AF showed a highly significant reduction in all-cause mortality with NOACs compared with warfarin (relative risk [RR] 0.90, 95% CI 0.85–0.95; p=0.0003) [8]. One NOAC, apixaban, was also superior to aspirin in reducing the risk of stroke with a lower risk of death, which was statistically insignificant. Collectively, however, these observations suggest that the effects of NOACs on mortality, compared with placebo, could be substantial but are presently uncertain. Demonstrating a clear mortality benefit of anticoagulation would reinforce the value of this therapeutic strategy in AF.

We have addressed this question in relation to apixaban as there are large randomized trials comparing this NOAC with both warfarin and aspirin, permitting indirect comparisons with a putative placebo derived from the aforementioned meta-analyses. Apixaban, a direct, selective factor Xa

inhibitor, was studied in 2 prospective randomized controlled trials in patients with AF at risk of stroke: Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) [4] and Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment (AVERROES) [9]. In ARISTOTLE, apixaban was compared with warfarin; AVERROES compared apixaban with aspirin. In both trials all-cause death was either a part of the hierarchical sequence of the primary analysis (ARISTOTLE) or a key secondary outcome (AVERROES). In each trial, rates of death were numerically lower with apixaban compared with the active control (warfarin or aspirin).

METHODS

We used the meta-analysis performed by Hart et al. [1] as a reference for the comparison between adjusted-dose warfarin and placebo/no treatment and between aspirin and placebo/no treatment. The ARISTOTLE trial was used for the comparison between apixaban and warfarin, and the AVERROES trial for the comparison between apixaban and aspirin. The outcome of interest for this analysis was all-cause death.

The protocols for both ARISTOTLE and AVERROES were approved by the ethics committee at each participating site, and all patients provided written informed consent before enrollment.

Adjusted-dose warfarin compared with placebo/no treatment

Hart et al. [1] pooled randomized trials that included patients with AF and investigated the efficacy of antithrombotic agents for stroke prevention in this population. Overall, 6 clinical trials that compared adjusted-dose warfarin with placebo/no treatment were identified, with a total of 2900 patients. The mean follow-up was 1.6 years.

Antiplatelet therapy compared with placebo/no treatment

In the same meta-analysis, 8 randomized trials compared antiplatelet therapies (aspirin and/or dipyridamole) with placebo/no treatment, and included a total of 4876 patients. The mean follow-up was 1.7 years. Of those, 7 trials (n=3990) compared aspirin alone with placebo/no treatment and accounted for 76% of follow-up exposure. For our mortality analysis, we used data from 5 trials that compared aspirin with placebo/no treatment and had mortality information available (n=3730). Among those studies, the aspirin dose varied from 75 mg daily to 325 mg daily.

The ARISTOTLE trial

The ARISTOTLE trial included 18,201 patients with AF and at least 1 additional risk factor for stroke—age ≥75 years, previous stroke/transient ischemic attack (TIA), symptomatic heart failure, diabetes, or hypertension. Participants were randomly assigned to apixaban 5 mg twice daily or dose-adjusted warfarin with a target international normalized ratio (INR) of 2.0 to 3.0. Apixaban 2.5 mg twice daily was given to participants with 2 or more of the following characteristics: age ≥80 years, body weight ≤60 kg, and serum creatinine ≥1.5 mg/dL. Key exclusion criteria included clinically significant mitral stenosis, prosthetic mechanical heart valve, previous intracranial bleeding, severe renal insufficiency, history of stroke within 7 days before randomization, and need for dual antiplatelet therapy. The median follow-up was 1.8 years.

The AVERROES trial

The AVERROES trial included 5599 patients with AF who were ≥50 years of age and had at least 1 additional risk factor for stroke—age ≥75 years, previous stroke/TIA, symptomatic heart failure, diabetes, hypertension, or peripheral artery disease. To be included, patients should have been considered unsuitable for treatment with a vitamin K antagonist. Participants were randomized to receive apixaban 5 mg twice daily or aspirin at a dose of 81 to 324 mg per day. Criteria for receiving a lower dose of apixaban were the same as for the ARISTOTLE trial. Key exclusion criteria included

valvular disease requiring surgery, high risk of bleeding, severe renal insufficiency, and need for dual antiplatelet therapy. The mean follow-up was 1.1 years. The AVERROES trial was stopped early by the data and safety monitoring board because of a clear benefit in favor of apixaban versus aspirin in the reduction of stroke or systemic embolism; therefore, this trial accrued only approximately half of the initially expected events.

Statistical analysis

Figure 1 shows the comparisons made in the schematic format. The indirect comparison method proposed by Bucher et al. [10] was used to estimate the odds ratio (OR) of apixaban compared with placebo. Using historical active control data for warfarin versus placebo reported by Hart et al., the OR of apixaban versus placebo was estimated as the ratio of the OR for apixaban versus warfarin and warfarin versus placebo. The CI for the OR was derived in the logit scale and based on the statistical independence of the estimates combined. A similar approach was used to derive the apixaban versus placebo OR, using the aspirin versus placebo information. The method used was similar to that used by Fisher et al. (using OR) [11] and McMurray et al. (using hazard ratio) [12]. The 2 ORs for apixaban versus placebo were then combined using a random effects model using the DerSimonian and Laird method, and the heterogeneity between trials was also tested.

This analysis assumes that the active control data (warfarin and aspirin) versus placebo estimate the same OR that would have occurred if the ARISTOTLE and AVERROES trials had included a placebo arm.

RESULTS

A summary of the study and patient characteristics in the Hart et al. meta-analysis, ARISTOTLE, and AVERROES is shown in **Table 1**. The mean age of participants was 70 years and was similar among patients included in the 3 studies. The meta-analysis of 6 trials that compared adjusted-dose warfarin with placebo/no treatment included a similar proportion of patients with previous stroke/TIA as the ARISTOTLE trial (20% and 19%, respectively). The meta-analysis of 8 trials that compared

antiplatelet therapy with placebo/no treatment included twice as many participants with previous stroke/TIA as the AVERROES trial (29% and 14%, respectively).

Apixaban, warfarin, and placebo

The number of deaths and death rates in the trials are compared in **Table 2**. In the Hart meta-analysis, a lower rate of death was seen with warfarin compared with placebo/no treatment (7.6% vs. 9.9%, OR 0.74, 95% CI 0.57–0.97) [1]. In ARISTOTLE, apixaban reduced the risk of death compared with warfarin (6.6% vs. 7.4%, OR 0.89, 95% CI 0.79–0.99) [4]. When compared with an imputed placebo, apixaban reduced the risk of death by 34% (95% CI 12–50%; p=0.004).

Apixaban, aspirin, and placebo

In the Hart meta-analysis, a numerically lower rate of death was seen with aspirin compared with placebo/no treatment (9.6% vs. 11.2%, OR 0.86, 95% CI 0.69–1.07) [1]. In AVERROES, apixaban tended to reduce the risk of death compared with aspirin (4.0% vs. 5.0%, OR 0.78, 95% CI 0.60–1.01) [9]. When compared with an imputed placebo, apixaban reduced the risk of death by 33% (95% CI 6–52%; p=0.02).

Apixaban versus placebo

Figure 2 summarizes the complete imputed placebo analysis. The overall estimate for a lower risk of death with apixaban compared with placebo is 34% (95% CI 18–47%; p=0.0002).

DISCUSSION

In a standard meta-analysis approach using data from previously published meta-analyses comparing warfarin with placebo and aspirin with placebo in the ARISTOTLE and AVERROES trials, we have demonstrated that apixaban reduces all-cause death by approximately one-third compared with placebo. While this method does not replace direct placebo-controlled studies, it implies that one may expect a large relative risk reduction in mortality when apixaban is used, rather than no therapy, in this patient population. This finding is particularly important because patients with AF have a

markedly elevated risk of death as well as stroke. Compared with warfarin, all NOACs resulted in numerically lower rates of death, and it is likely that all of them have a similar treatment effect on mortality when compared with placebo. The unique aspect of the apixaban program is that there were 2 large randomized trials (apixaban vs. warfarin; apixaban vs. aspirin). This allows an assessment of the effect of apixaban on mortality in patients with AF through a network meta-analysis of apixaban, warfarin, aspirin, and no antithrombotic therapy control.

Regulatory authorities usually require 2 positive placebo-controlled trials as evidence for approval of new treatments. However, once a therapy is definitely proven to be effective for a target disease, there may no longer be equipoise to randomize patients to placebo; thus, placebo-controlled trials may no longer be feasible or even ethical [13]. New therapies targeting the same therapeutic pathway must therefore be compared with the existing "gold standard." Of course this means that the direct effect of the new therapy compared with placebo is unknown. However, this can be addressed indirectly using historical data from the trials that compared the original gold standard with placebo [14]. This type of analysis may not provide enough evidence to justify a regulatory claim for the new agent, but it can help define the magnitude of the experimental drug effect on the outcome of interest. Ideally, in order to use this statistical approach, certain assumptions should be met. The populations and outcomes studied should be similar and the active control and reference trials should have used the same drug and in the same way. Overall, the meta-analysis and trials included in our analysis enrolled patients with AF and similar demographic profiles. The mean $CHADS_2$ score was similar among the ARISTOTLE and AVERROES studies. This risk score was not available at the time of trials comparing antithrombotic therapies with placebo. A considerable proportion of the participants in Hart et al. had previous history of stroke/TIA; thus, we may reasonably infer that these patients were also at high risk of stroke.

In ARISTOTLE and AVERROES, apixaban was used at a dose of 5 mg twice daily and the criteria for receiving a lower dose of apixaban were similar among these trials. In ARISTOTLE, dose-adjusted warfarin was given with a target INR of 2.0 to 3.0, and the median time in therapeutic range was 66% in warfarin-treated subjects. In Hart et al., the mean achieved INR ranged from 2.0 to 2.6 among warfarin-treated participants in 5 trials of primary prevention and was 2.9 in a single

secondary prevention trial. Regarding the aspirin dose, some differences among the studies should be highlighted. In AVERROES, the majority of participants (90.6%) received aspirin at a dose that ranged between 81 to 161 mg. In Hart et al., approximately half of the participants in trials that compared aspirin with placebo/no treatment received aspirin in a dose equal to or lower than 150 mg, whereas the other half received an aspirin dose of 300–325 mg. However, it has been previously shown that aspirin doses of 75–150 mg daily are at least as effective as higher doses for the prevention of ischemic events [15]. Thus, it is unlikely that the dose of aspirin played any role in our findings. Finally, since the effects of apixaban on reducing stroke versus warfarin and versus aspirin are clear, we elected to instead focus exclusively on its impact on mortality.

Patients with AF are at increased risk of stroke and systemic embolism. However, thromboembolic events do not lead to the majority of deaths observed in these patients. Several analyses have shown that most participants in clinical trials of AF died from other cardiovascular causes such as sudden cardiac death and heart failure [16-18]. Additionally, ICH is a devastating complication of anticoagulation therapy in this population, resulting in a fatality rate of 40–50% in the 30 days after ICH [19-21]. Moreover, in a study of older adults, premature death was the most common event within 5 years of a new diagnosis of AF; and, as expected, the risk of death was greater than the risk of stroke in this population [22]. Strategies to improve survival in patients with AF are needed. Management of cardiovascular risk factors and appropriate treatment of comorbidities may help improve survival in patients with AF. Oral anticoagulation is the mainstay for stroke prevention in patients with AF. We have observed that apixaban, as compared with warfarin, was effective in reducing mortality in patients with AF [4], and this effect versus no antithrombotic therapy was even greater when using indirect comparisons with a putative placebo. A possible explanation for the benefit of apixaban over warfarin on mortality is the reduction in bleeding events, particularly ICH [23]. We have shown that apixaban caused significantly less ICH than warfarin, regardless of type (spontaneous or traumatic) and location (intraparenchymal, subdural, or subarachnoid) [24]. It is also likely that by reducing stroke (and potentially myocardial infarction), apixaban might further reduce cardiovascular deaths. Thus, the impact of apixaban on mortality may be primarily due to cardiovascular causes, similar to what has been shown with other NOACs [16,18].

Our results must be interpreted in light of several limitations. We performed indirect comparisons and meta-analysis, and the statistical methods used do not replace the value of placebo-controlled trials. However, a placebo-controlled study in this clinical setting would not be feasible. Although the participants of the studies were demographically similar, we were unable to assess the $CHADS_2$ score in patients included in Hart et al.

CONCLUSION

A meta-analysis suggests that apixaban reduces all-cause death by 34% (18–47%) in comparison with an imputed placebo. Thus, in addition to preventing stroke among patients with AF and risk factors for stroke, there is evidence that apixaban substantially reduces mortality in these patients.

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JJVM and RDL had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. RDL, POG, and JJVM drafted the manuscript. All authors made substantial contributions to the design of the work and the acquisition, analysis, or interpretation of data; reviewed and revised the work; gave final approval of the version to be submitted; and agree to be accountable for all aspects of the work. The authors certify that the manuscript represents valid work and that neither this one nor one with substantially similar content under their authorship has been published or is being considered for publication elsewhere.

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LW: Institutional research grants from Bristol-Myers Squibb/Pfizer, AstraZeneca, Merck, Boehringer Ingelheim, and GlaxoSmithKline and consulting fees from GlaxoSmithKline, Bristol-Myers Squibb/Pfizer, Abbott, AstraZeneca, and Boehringer Ingelheim. KRL: Fees and expenses from Boehringer Ingelheim, EVER NeuroPharma, Nestle, Novartis but no external support in connection with this manuscript. JHA: Institutional research grants from Bristol-Myers Squibb, Boehringer Ingelheim, CSL Behring, National Institutes of Health, Sanofi, and Tenax Therapeutics and consulting fees from Bristol-Myers Squibb, CSL Behring, Duke Private Diagnostic Clinic, Pfizer, Portola, VA Cooperative Studies Program. JJVM: Institutional consulting fees from Novartis, Cardiorentis, Amgen, Oxford University/Bayer, GlaxoSmithKline, Theracos, Abbvie, DalCor, Pfizer, and Merck.

Ethical Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

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Figure Legends

Figure 1. Title: Analysis design. Caption: Schematic of the trials and comparisons used in the putative placebo analysis.

Figure 2. Title: Odds ratio plot. Caption: Treatment effect of apixaban in all-cause death in putative placebo analysis.

Table 1. Selected characteristics of trials and participants

	Hart et al.[1]		ARISTOTLE	AVERROES
Treatments	Adjusted-dose warfarin vs. placebo/ no treatment	Antiplatelet therapy vs. placebo/ no treatment	Apixaban vs. warfarin	Apixaban vs. aspirin
Year of publication	2007	2007	2011	2011
Number of trials	6	8	-	-
Number of participants	2900	4876	18201	5599
Follow-up (years)	1.6	1.7	1.8	1.1
Participants				
Age (yrs)	69	69	70	70
Female (%)	29	37	35	41
Previous stroke/TIA (%)	20	29	19	14
Hypertension (%)	-	-	87.5	86.4
Diabetes (%)	-	-	25.0	20.0
$CHADS_2$	-	-	2.1	2.1

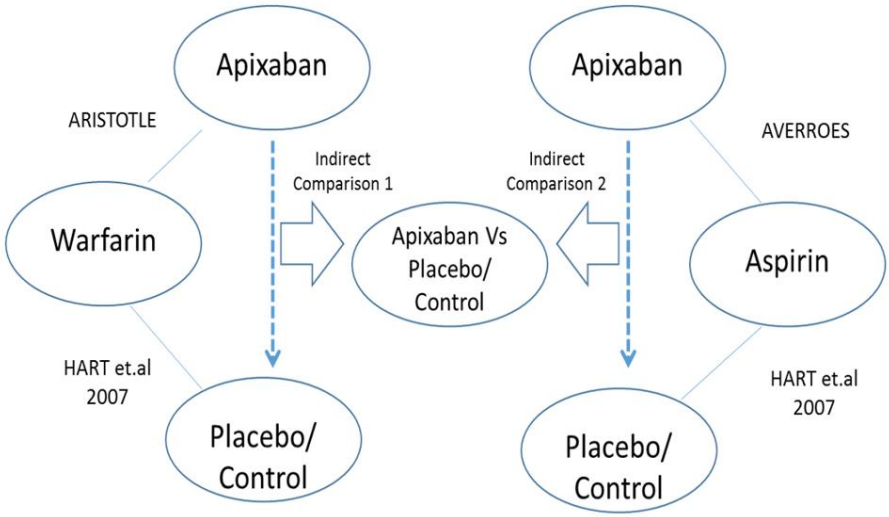
TIA=transient ischemic attack.

Table 2. Number of deaths and death rates in trials

Apixaban vs. Placebo using Warfarin as Active Control						
	Apixaban*	**Warfarin***	**Placebo***	**Comparison**	**OR (95% CI)**	**p-value**
ARISTOTLE	603/9120 (6.6)	669/9081 (7.4)	--	Apixaban vs. Warfarin	0.890 (0.794–0.998)	
Hart et al.(1)	--	110/1450 (7.6)	143/1450 (9.9)	Warfarin vs. Placebo	0.740 (0.570–0.970)	
Indirect estimate				Apixaban vs. Placebo	0.659 (0.495–0.876)	0.004
Apixaban vs. Placebo using Aspirin as Active Control						
	Apixaban	**Aspirin**	**Placebo**	**Comparison**	**OR (95% CI)**	**p-value**
AVERROES	111/2807 (4.0)	140/2791 (5.0)	--	Apixaban vs. Aspirin	0.780 (0.604–1.006)	
Hart et al.(1)	--	184/1912 (9.6)	204/1818 (11.2)	Aspirin vs. Placebo	0.860 (0.690–1.070)	
Indirect estimate				Apixaban vs. Placebo	0.670 (0.479–0.939)	0.020
Apixaban vs. Placebo Combined						
Indirect estimate				Apixaban vs. Placebo†	0.664 (0.534–0.825)	0.0002

*Cells contain number of deaths / number of patients (% of patients)
†Heterogeneity p-value: 0.959.
CI=confidence interval; OR=odds ratio.

Figure 1.


Apixaban
ARISTOTLE
Warfarin
HART et.al
2007
Placebo/
Control
Indirect
Comparison 1
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Comparison 2
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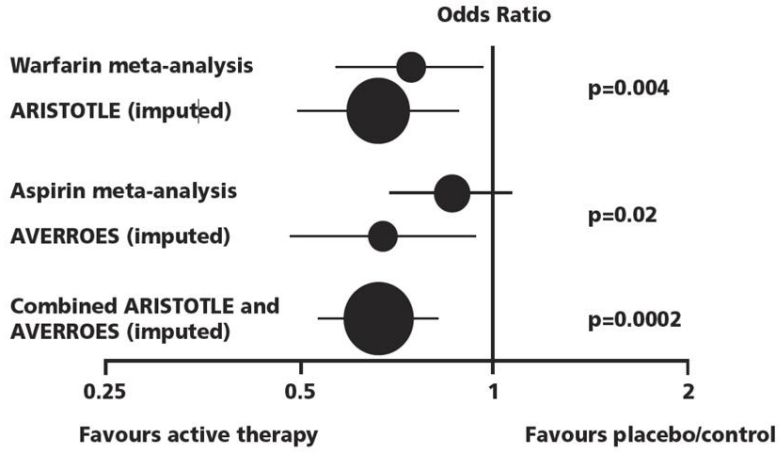
Aspirin
HART et.al
2007
Placebo/
Control

Figure 2.


Odds Ratio
Warfarin meta-analysis
ARISTOTLE (imputed)
p=0.004
Aspirin meta-analysis
AVERROES (imputed)
p=0.02
Combined ARISTOTLE and AVERROES (imputed)
p=0.0002
0.25
0.5
1
2
Favours active therapy
Favours placebo/control