JACC: CLINICAL ELECTROPHYSIOLOGY
VOL. 2, NO. 1, 2016

ISSN 2405-500X/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jacep.2015.09.015

Net Clinical Benefit of Edoxaban for Stroke, Mortality, and Bleeding Risk

Modeling Projections for a European Population

Andrew D. Blann, PhD,[a] Ron Pisters, PhD,[b] Gregory Y.H. Lip, MD[a,c]

ABSTRACT

OBJECTIVES The purpose of this study was to determine, in a model based on Europeans at risk of stroke by virtue of atrial fibrillation (AF), the net clinical benefit of edoxaban in the reduction of the risk of stroke, mortality, and of hemorrhage.

BACKGROUND Vitamin K antagonists (e.g., warfarin) are commonly underused because of such factors as fear of hemorrhage in patients with high-risk AF. The non-vitamin K antagonist oral anticoagulants are similarly or more effective than warfarin and have lower rates of serious hemorrhage. Although outcomes of the ENGAGE AF-TIMI 48 trial that compared the non-vitamin K antagonist oral anticoagulant edoxaban with warfarin and indicated similar efficacy and better safety compared with warfarin for stroke prevention in AF, the application of trial data to the general population is unknown.

METHODS This study modelled a treatment effect of edoxaban on the risks of thromboembolism, major bleeding, and death in a real-world population of patients with AF drawn from the Euro Heart Survey, and extrapolated this to the general European population.

RESULTS In those at high risk of stroke ($CHA_2DS_2VASc \geq 2$), edoxaban would need to be taken by 319 patients to prevent 1 thromboembolism, major bleeding event, or death compared with warfarin, and by 41 patients to prevent 1 thromboembolism or death compared with no treatment. These translate to demonstrating a net clinical benefit of 8.9 events saved per 1,000 patients with edoxaban 60 mg. Modeling these data to the population of Europe of 508 million, use of edoxaban 30 mg and 60 mg instead of warfarin would, respectively, prevent approximately 19,400 and 30,300 thromboembolic events, major bleeds, and deaths annually.

CONCLUSIONS Our modeling exercise suggests that the use of edoxaban for thromboprophylaxis in AF based on current guidelines could provide a profound benefit on rates of stroke, major bleeds, and deaths in European patients with AF. (J Am Coll Cardiol EP 2016;2:47–54) © 2016 by the American College of Cardiology Foundation.

Nonvalvular atrial fibrillation (AF) brings a risk of ischemic stroke and systemic embolism. In an individual patient, the risk of such an event can be quantified by the sum of certain common clinical and demographic factors, these being the presence of congestive heart failure, hypertension, age 65 to 74 or ≥75 years, diabetes, stroke or transient ischemic attack (TIA), female sex, and

From the [a]University of Birmingham Institute of Cardiovascular Sciences, City Hospital, Birmingham, United Kingdom; [b]Department of Cardiology, Maastricht University Medical Centre, Maastricht, the Netherlands; and the [c]Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark. This study was funded by an unrestricted educational grant from Daiichi Sankyo. Dr. Blann has received funding for research from Boehringer Ingelheim; and has been on the speaker bureaus for Bayer, BMS/Pfizer, and Boehringer Ingelheim. Dr. Pister has received fees for serving on advisory boards from Pfizer and Bristol-Myers Squibb; and has received honoraria from Bayer, Daiichi Sankyo, Pfizer, and Bristol-Myers Squibb. Prof. Lip has served as a consultant for Bayer/Jensen J&J, Astellas, Merck, AstraZeneca, Sanofi, BMS/Pfizer, Biotronik, Medtronic, Portola, Boehringer Ingelheim, Microlife, and Daiichi Sankyo; performed guideline membership/reviewing for various guidelines and position statements from European Society for Cardiology, European Heart Rhythm Association, and National Institute of Health and Care Excellence; served on the steering committee for various phase II and III studies, Health Economics & Outcomes Research; was an investigator in various clinical trials in cardiovascular disease, including those on antithrombotic therapies in atrial fibrillation, acute coronary syndrome, and lipids; and was a speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche, and Daiichi Sankyo.

Manuscript received July 20, 2015; revised manuscript received September 14, 2015, accepted September 17, 2015.

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

CHA_2DS_2-VASc = congestive heart failure, hypertension, age 65 to 74 or ≥75 years, diabetes, stroke or transient ischemic attack, vascular disease, sex category

CI = confidence interval

HAS-BLED = hypertension, abnormal liver/renal function, stroke or thromboembolism, bleeding history or predisposition, labile international normalized ratio, elderly, and use of certain drug therapies

HR = hazard ratio

NCB = net clinical benefit

NNT = number needed to treat

NOAC = non-vitamin K antagonist oral anticoagulant

OAC = oral anticoagulant

RRR = relative risk reduction

TIA = transient ischemic attack

VKA = vitamin K antagonist

other vascular disease, known as the CHA_2DS_2-VASc score (1). The greater the CHA_2DS_2-VASc score, the greater the risk of thromboembolism. The most effective treatment of the risk of ischemic stroke and systemic embolism in AF is oral anticoagulation (OAC), most commonly with the vitamin K antagonist (VKA) warfarin (2). However, OAC also brings risk of hemorrhage (3), the risk of which in an individual can be quantified by a second scoring system, the HAS-BLED score (4). This score sums hypertension, abnormal liver/renal function, stroke or thromboembolism, bleeding history or predisposition, labile international normalized ratio (for those on warfarin), elderly (age >65 years), and use of certain drug therapies or alcohol abuse (4). The greater the HAS-BLED score, the greater the risk of hemorrhage.

The concept of net clinical benefit (NCB) has been used to quantify the balance between a reduced risk of thrombosis (e.g., ischemic stroke and systemic embolism) compared with an increased risk of bleeding (e.g., intracranial hemorrhage) with warfarin in AF (5). Patients with the highest risk of ischemic stroke and systemic embolism (i.e., a high CHA_2DS_2-VASc) have the greatest NCB of warfarin at both low (HAS-BLED ≤2) and high (HAS-BLED ≥3) risk of hemorrhage (6). These scoring systems have been used to explore the NCBs of 3 non-VKA oral anticoagulants (NOACs) dabigatran (7), rivaroxaban (8), and apixaban (9) in a "real world" setting (i.e., outside clinical trials), which concluded that these NOACs seem to have a superior NCB (in terms of the number of major cardiovascular events saved) than does warfarin (10).

Edoxaban is a new anti-factor Xa NOAC approved for the prevention of stroke and systemic embolism in patients with nonvalvular AF in the United States, Europe, and Japan and is undergoing regulatory consideration in other countries. At doses of 30 mg or 60 mg daily, edoxaban is noninferior in protecting against ischemic stroke/thromboembolism in AF, and is associated with less major bleeding and death from cardiovascular causes compared with warfarin (11). We have used network meta-analysis and other modeling to determine the NCB of edoxaban in patients with different CHA_2DS_2-VASc and HAS-BLED scores, to indirectly compare edoxaban with the other NOACs and imputed placebo, and to estimate the potential NCB of edoxaban for Europeans with AF (10,12–14). A danger of this approach is that data derived from clinical trials may not be accurately extrapolated to a nonclinical trial population, because the former are likely to be healthier (e.g., with fewer comorbidities) than the general population.

Using the same data, analysis, and modeling from the Euro Heart Survey (6,14,15) and the ENGAGE AF-TIMI 48 (Effective aNticoagulation with factor xA next GEneration in Atrial Fibrillation-Thrombolysis In Myocardial Infarction 48) trial (11), we set out to model a treatment effect of edoxaban on the risks of thromboembolism, major bleeding, and death in a real-world population of patients with AF drawn from the Euro Heart Study, and also extrapolated this to the general European population.

METHODS

STUDY POPULATION. The fine details of the Euro Heart Survey, comprising data from 5,333 real-world patients with AF from 182 hospitals in 35 countries, from whom the full spectrum of CHA_2DS_2-VASc and HAS-BLED factors were collected, have been described (6,14). To determine the relationship between CHA_2DS_2-VASc and HAS-BLED score and outcome, the following endpoints were focused on: 1) the combined endpoint of thromboembolism, ischemic stroke, TIA, and systemic (outside the heart, brain, eyes, and lungs) embolic events; 2) the combined endpoint of hemorrhagic stroke and other major bleeding (requiring hospitalization and/or a drop in hemoglobin of 20 g/l or more [16], and/or requiring blood transfusion); and 3) all-cause mortality (16). These criteria are broadly in common with the hemorrhage criteria of the ENGAGE AF-TIMI 48 trial of edoxaban that compared with warfarin (11), and trials of other NOACs compared with warfarin (7–9).

After a year, robust data were available on 2,788 patients who at baseline were eligible for antithrombotic treatment (15). Baseline $CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED factors, treatment, and the rates of thromboembolism, major bleeding, and death are shown in **Table 1**, stratified by their CHA_2DS_2-VASc score of ≥1 and ≥2. Considering the relatively insignificant stroke prevention of antiplatelet agents in patients with AF, we combined all patients taking antiplatelets with patients not on any antithrombotic therapy into a single comparator group (i.e., no OAC) to be compared with all those taking OAC (i.e., warfarin). **Table 2** shows the rates of thromboembolism, major bleeding, and death according to use of high or low edoxaban doses and by risk of stroke (i.e., CHA_2DS_2-VASc score).

MODEL ASSUMPTIONS AND EVENT RATES. We followed the same modeling process as per our

TABLE 1 Baseline Characteristics of Patients With NVAF in the Euro Heart Survey Modeling Analysis Who Were Eligible for Treatment, Use of Oral Anticoagulant, and 1-Year Outcome Stratified by Their CHA_2DS_2-VASc Score

	CHA_2DS_2-VASc ≥1 (n = 2,788)	CHA_2DS_2-VASc ≥2 (n = 2,290)
Baseline factors		
Age, yrs	68.5 ± 11.3	71.1 ± 9.6
Female	1,227 (44)	1,131 (49)
Hypertension	2,009 (72)	1,787 (78)
Heart failure	858 (31)	802 (35)
Coronary artery disease	798 (29)	768 (34)
Diabetes mellitus	533 (19)	527 (23)
Previous stroke/TIA	315 (11)	315 (14)
$CHADS_2$ score	1.8 ± 1.2	2.0 ± 1.2
CHA_2DS_2-VASc score	3.19 ± 1.7	3.67 ± 1.4
HAS-BLED score	1.2 ± 0.9	1.3 ± 0.9
Treatment		
Oral anticoagulation	1,807 (65)	1,481 (65)
No oral anticoagulant	981 (35)	809 (35)
Follow-up		
Thromboembolism	89 (3.19)	72 (3.14)
Major bleeding	42 (1.51)	34 (1.48)
Death	120 (4.30)	98 (4.28)

Values are mean ± SD or n (%).

$CHADS_2$ = congestive heart failure, hypertension, age ≥75 years, diabetes, and stroke or transient ischemic attack; CHA_2DS_2-VASc = congestive heart failure, hypertension, age 65 to 74 or ≥75 years, diabetes, stroke or transient ischemic attack, female, and other vascular disease; HAS-BLED = hypertension, abnormal liver/renal function, stroke or thromboembolism, bleeding history or predisposition, labile international normalized ratio (for those on warfarin), elderly (age >65 years), and use of certain drug therapies or alcohol abuse; NVAF = non-valvular atrial fibrillation; TIA = transient ischemic attack.

TABLE 2 The Number Needed to Treat and the Number of Potentially Preventable Thromboembolism, Major Bleeding, and Deaths With the Use of Edoxaban Versus Oral Anticoagulation or No Oral Anticoagulation in the Euro Heart Survey on AF

	Thromboembolism*		Major Bleeding†		Death‡	
	Rate (%)	NNT	Rate (%)	NNT	Rate (%)	NNT
CHA_2DS_2-VASc score ≥1 N = 2,788§						
OAC (n = 1,807)§	2.80	Ref.	1.90	Ref.	4.20	Ref.
Edoxaban 30 mg‖	3.93	−89	0.89	99	3.67	189
Edoxaban 60 mg‖	2.72	1,250	1.52	263	3.85	286
No OAC (n = 981)§	3.00	Ref.	1.60	Ref.	4.40	Ref.
Edoxaban 30 mg¶	1.25	57	NA	NA	2.43	51
Edoxaban 60 mg¶	0.97	49	NA	NA	2.57	54
CHA_2DS_2-VASc score ≥2 N = 2,290§						
OAC (n = 1,481)§	2.80	Ref.	2.10	Ref.	4.70	Ref.
Edoxaban 30 mg‖	3.93	−89	0.99	90	4.11	169
Edoxaban 60 mg‖	2.72	1,250	1.68	238	4.31	256
No OAC (n = 809)§	4.00	Ref.	1.40	Ref.	5.40	Ref.
Edoxaban 30 mg¶	1.67	43	NA	NA	2.98	41
Edoxaban 60 mg¶	1.29	37	NA	NA	3.15	44

*The combined endpoint of thromboembolism, being ischemic stroke, transient ischemic attack, and systemic (outside the heart, brain, eyes, and lungs) embolic events (15). †The combined endpoint of hemorrhagic stroke and other major bleeding (e.g., that requiring hospitalization and/or a drop in hemoglobin of 20 g/l or more, and/or requiring blood transfusion) (15). ‡Any cause death. §From reference (15). ‖Imputed from reference (11). ¶Imputed from reference (13).

AF = atrial fibrillation; NA = data from which to estimate rate of major bleeding are unavailable; NNT = number needed to treat; no OAC = no antithrombotic treatment or treatment with aspirin; OAC = oral anticoagulant (warfarin); Ref. = reference; other abbreviations as in Table 1.

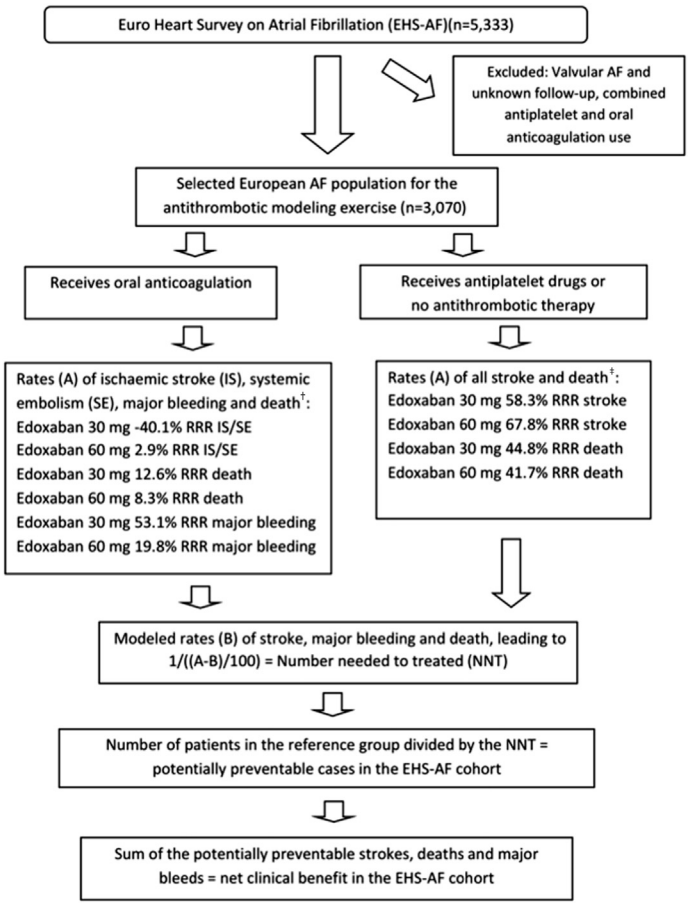
previous analyses (10,12,14). These were the rates of observed thromboembolism, major bleeding, and all-cause death from the Euro Heart Survey modeling analysis (15) (**Table 1**), and the calculated hazard ratios (HRs) plus 95% confidence intervals (CIs) for the effect of edoxaban 30 mg and 60 mg versus warfarin on the rates of ischemic stroke and systemic embolic event combined (= thromboembolism), and on the rates of major bleeding (which included any intracranial bleeding and overt bleeding with blood loss >20 g/l) (16) based on the %patient/year data from the ENGAGE AF-TIMI 48 trial (11). However, in ENGAGE, the high-dose regimen was 60 mg and dose reduced to 30 mg for certain factors (renal function, low body weight), and the low-dose regimen was 30 mg and dose reduced to 15 mg for certain factors.

Compared with patients treated with warfarin, edoxaban 60 mg brought a HR of 0.971 (95% confidence interval [CI]: 0.80 to 1.19) for thromboembolism (ischemic stroke and systemic embolic event), which translates to a relative risk reduction (RRR) of 2.9% (11). The HR of major bleeding was 0.802 (95% CI: 0.71 to 0.91), that being a RRR of 19.8%, and a HR of 0.917 (95% CI: 0.83 to 1.01) for any cause death, a RRR of 8.3%. Similarly, edoxaban 30 mg brought a HR of 1.401 (95% CI: 1.15 to 1.71) for ischemic stroke and systemic embolism, a RRR of −40.1% (i.e., an increased risk of these events); a HR of major bleeding 0.469 (95% CI: 0.41 to 0.55), a RRR of 53.1%; and a HR of 0.874 (95% CI: 0.79 to 0.96) for any cause death, a RRR of 12.6%.

Although none of the NOACs have been formally studied against placebo for the prevention of stroke or systemic embolism in AF, Verdecchia et al. (13) performed an imputed-placebo analysis with estimates of the proportion of warfarin effect by each of the NOACs, drawing on data from clinical trials with warfarin as the common comparator (7–9,11). They estimated that use of edoxaban 30 mg would, compared with imputed placebo, bring an odds ratio for the risk of all stroke of 0.417 (95% CI: 0.29 to 0.60), and so a RRR of 58.3%. Similarly, edoxaban 60 mg would bring an odds ratio for the risk of all stroke of 0.322 (95% CI: 0.22 to 0.47), and a RRR of 67.8% compared with imputed placebo. **Figure 1** displays the modeling process in a flow chart.

NUMBER NEEDED TO TREAT. The number of patients needed to treat (NNT) to prevent 1 ischemic stroke or

FIGURE 1 Flow Chart of Modeling Procedure*



*Modeling flow chart from reference 15. †From reference 11. ‡From reference 13. RRR = relative risk reduction.

systemic embolism, 1 hemorrhagic stroke or major bleed, or any-cause death per 100 patient-years was calculated as: (1/absolute risk reduction) × 100, where absolute risk reduction was absolute reduction, that is, the event rate observed in the Euro Heart Survey minus the assumed event rate on edoxaban (10,15). A negative value for NNT denotes the number needed to harm, that is, the NNT in order to cause 1 major bleed (10).

NET CLINICAL BENEFIT. The NCB of edoxaban compared with warfarin was calculated first using the following formula: [(rate of ischemic stroke and systemic embolism on warfarin minus the rate of ischemic stroke and systemic embolism on edoxaban) − 1.5 × (rate of major bleeding rate on edoxaban − the rate of major bleeding rate on warfarin)] (5,6,10). Because the Singer et al. (5) equation does not include mortality, therefore, we also present an additional simple and more pragmatic NCB that includes death, that being the sum of cases (saved or caused) of thromboembolism, major bleed (which is unweighted and absolute), and death (15). The number needed to benefit in 1,000 patients is 1,000/NCB.

EXTRAPOLATION TO EUROPE. On January 1, 2014, the Eurostat agency of the European Union estimated the population of its 28 member states to be 506,880,616 (17). The population increased by 0.2% from 2012 to 2013 and by 0.35% from 2013 to 2014. We therefore estimate the population in 2015 to be 0.27% higher, that is, 508,192,935 people. To counter a potential overestimation of the benefits of NOACs, we assumed a conservative AF prevalence of 1%, being the low end of the widely reported rate of 1% to 2% (18), which predicts a population of approximately 5,081,929 Europeans with AF. We also assumed a similar distribution of stroke risk factors and the use of antithrombotic therapy based on the established ability of the Euro Heart Study to represent European patients with AF and report on AF in primary care (12,19). This predicts 82% of patients to have a CHA_2DS_2-VASc score ≥1, and 67% to have a CHA_2DS_2-VASc score ≥2 (i.e., with a high risk of stroke, with a clear indication for OAC) (15). This in turn translates to European AF population estimates of 4,167,182 patients who would therefore be potentially eligible for OAC treatment, of which 3,404,893 would be at high risk.

STATISTICAL ANALYSIS. SPSS statistical software version 17.0 (SPSS Inc., Chicago, Illinois) was used to perform data analysis. Continuous variables are reported as mean ± SD and categorical variables as number of observed patients (percentage). Rates of cardiovascular events and death are expressed as HR or odds ratio with 95% CIs.

RESULTS

Table 2 shows the rates of thromboembolism, major bleeding, and death, and the NNTs of the Euro Heart Survey patients with AF on OAC, those not on OAC, and calculated rates if on edoxaban 30 mg or 60 mg stratified by CHA_2DS_2-VASc score (15).

In the entire cohort of 2,788 patients with a CHA_2DS_2-VASc score ≥1 (Table 2, top), the rates of thromboembolism (RRR: 6.7%) and death (RRR: 4.5%) are lower in those 1,807 patients on OAC, but major bleeding is higher (RRR: −18.75%), compared with those 981 patients on no OAC. Our model predicts that use of edoxaban 30 mg in our population increases the rate of thromboembolism by 1.13%, reduces the rate of major bleeding by 1.01%, and

reduces the rate of death by 0.53% compared with those taking OAC. In those not taking OAC, edoxaban 30 mg would have reduced the rate of thromboembolism by 1.75% and the rate of death by 1.97%. The Verdecchia et al. (13) analysis did not investigate hemorrhage, so no comparisons can be made. Use of edoxaban 60 mg in our population would have reduced the rate of thromboembolism by 0.08%, reduced the rate of major bleeding by 0.38%, and reduced the rate of death by 0.35% compared with those taking OAC. In those not taking OAC, edoxaban 60 mg would have reduced the rate of thromboembolism by 2.03% and of death by 1.84%.

These effects are generally more pronounced in the 2,290 patients with a CHA_2DS_2-VASc score ≥2 (**Table 2**, bottom), where OAC is again linked to less thromboembolism (RRR: 30%) and death (RRR: 13%) but with a higher rate of major bleeding (RRR: −50%) than no OAC. Use of edoxaban 30 mg would once more have increased the rate of thromboembolism by 1.13%, reduced the rate of major bleeding by 1.12%, and reduced the rate of death by 0.6% compared with those taking OAC. In those not taking OAC, edoxaban 30 mg would have reduced the rate of thromboembolism by 2.33% and the rate of death by 2.42%. Similarly, use of edoxaban 60 mg in those taking an OAC would have reduced the rate of thromboembolism by 0.08%, reduced the rate of major bleeding by 0.42%, and reduced the rate of death by 0.39%. In those not taking OAC, edoxaban 60 mg would have reduced the rate of thromboembolism by 2.71% and the rate of death by 2.25%.

Thus the overall crude beneficial effect of edoxaban compared with the use of OAC in terms of mean NNT to prevent 1 thromboembolism, major bleed, or death would be greater in the high-risk population (CHA_2DS_2-VASc score ≥2) with a smaller NNT (n = 319) compared with a low-risk group of patients with CHA_2DS_2-VASc score ≥1 (n = 333). Similarly, the overall crude beneficial effect of edoxaban compared with the use of no OAC in terms of mean NNT to prevent 1 thromboembolism or death would be greater in the high-risk population (CHA_2DS_2-VASc score ≥2) with a smaller NNT (n = 41) compared with a low-risk group of patients with CHA_2DS_2-VASc score ≥1 (n = 53).

Table 3 shows the projected number of events saved or caused by the use of edoxaban 30 mg once daily or edoxaban 60 mg once daily in place of warfarin, the NCB in 1,000 patients with AF in the Euro Heart Survey modeling analysis. The balance between the thromboembolic events caused or prevented and the adjusted number of major bleeds caused or prevented gives the NCB according to Singer et al. (5) and its associated number needed to benefit. **Table 3** also shows the number of deaths saved, which when added to the thromboembolisms and major bleeds gives the NCB according to Pisters et al. (15) (i.e., all events), and an associated number needed to benefit. With the exception of the increased number of thromboembolic events with edoxaban 30 mg once daily, both doses of edoxaban were more beneficial (higher NCB and lower number needed to benefit) in the high-risk patients (CHA_2DS_2-VASc score ≥2) compared with patients with CHA_2DS_2-VASc score ≥1.

EXTRAPOLATION TO EUROPE. Thus far, the analysis has been based on 3,400 patients in the EHS-AF Survey modeling analysis eligible for OAC, of whom 2,290 (67%) were at high risk of stroke (i.e., CHA_2DS_2-VASc score ≥2). Assuming the EHS-AF population is representative of all Europeans, there are approximately 4.167 million Europeans eligible for OAC, of whom 3.404 million are at high risk of stroke. Multiplying the rate of events saved per 1,000 patients with these populations gives the number of separate events saved (as thromboembolisms, major bleeds, and deaths) per year in Europe (**Table 3**).

In combining these 3 groups of endpoints (thromboembolism, major bleed, death), use of edoxaban 30 mg in place of warfarin would prevent more than 17,000 major events each year in the CHA_2DS_2-VASc score ≥1 group and more than 19,400 events in the CHA_2DS_2-VASc score ≥2 group. Similarly, use of edoxaban 60 mg in place of warfarin would prevent in excess of approximately 33,000 events in the CHA_2DS_2-VASc score ≥1 group and more than 30,000 events in the CHA_2DS_2-VASc score ≥2 group.

DISCUSSION

The risk of stroke is significantly increased in patients with AF, and this risk can be markedly reduced with the use of a potent group of oral anticoagulants (i.e., the VKAs). Nevertheless, the numerous disadvantages of VKAs, which include an increased risk of gastrointestinal and intracranial hemorrhage, and many food and drug interactions (2,3), have prompted some practitioners to offer alternatives, such as antiplatelet therapy, or even (for those, such as the elderly, considered to be at the highest risk of hemorrhage) no treatment (20–22).

However, antiplatelet agents bring little or no reduction in the risk of stroke but do bring an increased risk of hemorrhage (4,23). These and other issues prompted the development of the NOACs, which as a class are dependent on dose and patient

risk, but are generally of similar or better efficacy compared with VKAs, with better safety profiles (7-9,11). In support of this assertion, our data with a Danish nationwide cohort showed a superior NCB of apixaban, dabigatran, and rivaroxaban compared with warfarin in patients with AF with a CHA_2DS_2-VASc score ≥1 (10). In extrapolating these data to Europe, our previous model predicts that dabigatran and apixaban would save thousands of cardiovascular events (15). The validity of this modeling approach is supported by data on the effects of other NOACs versus VKA from real-world observational studies (24,25).

In this analysis, we investigate the potential benefit of using the NOAC edoxaban and the impact of this on patients with AF with ≥1 and ≥2 of CHA_2DS_2-VASc stroke risk factors, if this drug were given to all patients with AF on no treatment or an antiplatelet, or as a substitute for antithrombotic management with a VKA. This theoretical management of the replacement of warfarin could potentially result in the Singer et al. (5) NCB of thromboembolism and major bleeds prevented in around 3.9 people per 1,000 treated at the 30-mg dose of edoxaban, dependent on their risk of stroke. Similarly, the 60-mg dose would save an event in 6.5 people per 1,000 treated, dependent on stroke risk. However, the Singer method for calculating NCB, developed to counter the excess risk of bleeding by warfarin, so placing additional weight on hemorrhage, does not include death (5). Thus, by simply taking the sum of thromboembolism, major bleeds, and death (15), the 30-mg dose of edoxaban would result in a Pisters et al. (15) NCB of around 4.1 events saved per 1,000 patients with AF, whereas the 60-mg dose would also bring a greater NCB of around 8.1 events saved (dependent on risk score) and a concurrent reduction in the overall number needed to benefit.

Extending this modeling exercise throughout the whole of Europe (with a population of some 508 million) by means of extrapolating the results would translate to the additional prevention of between approximately 17,000 and 33,000 major cardiovascular events (stroke, thrombosis, major bleeds, and death) per year, dependent on the dose of edoxaban and the risk of stroke. This analysis underlines and extends (10,15) the importance of a risk profile-based approach (i.e., CHA_2DS_2-VASc) when prescribing edoxaban to maximize the potential benefit.

STUDY LIMITATIONS. We note several limitations of this analysis, the most important being the assumptions required to calculate the rates of thromboembolism, major hemorrhage, and death. Of these, perhaps the most relevant assumption is that the rates of thromboembolism, major bleeding, and death can

TABLE 3 Number of Events Saved, Net Clinical Benefit, and Number Needed to Benefit From the Use of Edoxaban Compared With Warfarin in a European Population

	Edoxaban 30 mg od	Annual Number of Events Saved (Caused) in Europe	Edoxaban 60 mg od	Annual Number of Events Saved (Caused) in Europe
All eligible patients (CHA_2DS_2-VASc ≥1), N = 4.167 million				
Thromboembolic events saved*	−11.3	−47,087	0.8	3,334
Major bleeds saved†	10.1	42,087	3.8	15,835
Net clinical benefit (excluding deaths)‡	3.9		6.5	
Number needed to benefit (excluding deaths)	260.0		154	
Deaths saved§	5.3	22,085	3.5	14,585
Net clinical benefit (including deaths)‖	4.1	17,085	8.1	33,754
Number needed to benefit (including deaths)	244.0		123	
High-risk patients (CHA_2DS_2 -VASc ≥2), N = 3.404 million				
Thromboembolic events saved*	−11.3	−38,465	0.8	2,723
Major bleeds saved†	11.1	37,784	4.2	14,297
Net clinical benefit (excluding deaths)‡	5.4		7.1	
Number needed to benefit (excluding deaths)	185.0		141	
Deaths saved§	5.9	20,084	3.9	13,276
Net clinical benefit (including deaths)‖	5.7	19,403	8.9	30,296
Number needed to benefit (including deaths)	175.0		112	

Number of events saved and net clinical benefit adjusted to 1,000 patients with AF. *The combined endpoint of thromboembolism is a composite of ischemic stroke, transient ischemic attack, and systemic embolic events. †The combined endpoint of hemorrhagic stroke and other major bleeding (e.g., that requiring hospitalization and/or a drop in hemoglobin of 20 g/l or more, and/or requiring blood transfusion). ‡Net clinical benefit per 1,000 patients calculated from the balance of thromboembolic events (saved-caused) − weighted major bleeds (saved-caused) (5). §Any-cause death. ‖The sum of each of the following (saved-caused): thromboembolisms, major bleeds, and deaths (15).

od = once daily; other abbreviations as in Table 1.

be extrapolated from the ENGAGE AF-TIMI 48 trial (11) and modelled into the Euro Heart Survey database (15). Caution is warranted because different risk factor prevalence rates that lead to estimates of preventable events are not necessarily transferable from randomized clinical trials to real world patients in a clinical setting (26). For example, 38.1% of ENGAGE AF-TIMI 48 trial (11) patients were women, compared with 42.1% of the Euro Heart Survey patients (15). There are also differences in age (median 72 years, mean 66.5 years, respectively), rate of heart failure (57.4%, 33.7%), diabetes mellitus (36.1%, 18.1%), and stroke/TIA (28.3%, 10.7%), leading to a difference in the mean $CHADS_2$ score of 2.8 ± 1.0 in ENGAGE AF-TIMI 48 and 1.8 ± 1.2 in the Euro Heart Survey (11,14,15).

In ENGAGE, the high-dose regimen of 60 mg was reduced to 30 mg for certain clinical factors, whereas the low-dose regimen of 30 mg was reduced to 15 mg for certain clinical factors. The data here and throughout for 30 mg are for the 30 mg once daily dose (including doses reduced to 15 mg). This is so as to not confuse it with the patients in the 60-mg arm who received 30 mg because of renal function, low body weight, or Pg-P inhibitor use. We cannot determine the degree of warfarin anticoagulation control in the various groups and assume they are equal: it is possible that international normalized ratio control is less rigorous in the community than in a clinical trial, and this may have an impact on outcomes (27,28). The equation of Singer et al. (5) simply balances risk of ischemic stroke and other systemic emboli with those of any intracranial hemorrhage, and did not include a sudden neurological deficit lasting <24 h (i.e., a TIA). The Verdecchia et al. (13) analysis pooled ischemic and hemorrhagic strokes, so these estimates versus placebo may also be incorrect. The endpoints of the Euro Heart Survey modeling analysis (15) also included TIA and peripheral embolism (outside the heart, brain, eyes, and lungs), whereas major bleeding was hemorrhagic stroke and bleeding in other organs. These differences may lead to some inconsistencies in interstudy comparisons of modeling data.

CONCLUSIONS

Based on this modeling analysis of NCB, edoxaban is preferable to warfarin and no treatment for all those with AF requiring OAC, and the effect is more marked in those at high risk of stroke. Although this effect may be true for all NOACs, our data clearly show the positive effect of edoxaban, and practitioners need to determine which NOAC is best fitted to their patient (taking into account their variable clinical profile), and vice versa. In this respect, the lower dose of edoxaban (30 mg) may be preferred in those with moderate renal function (29). Nevertheless, in this group, use of edoxaban 30 mg in place of warfarin throughout Europe would save approximately 18,000 combined thromboembolisms, major bleeds, and deaths, whereas the 60-mg dose would save about 32,000 such events each year.

ACKNOWLEDGMENT The authors thank Brad Zerlanko for helpful comments.

REPRINT REQUESTS AND CORRESPONDENCE: Prof. Gregory Y.H. Lip, University of Birmingham Institute of Cardiovascular Sciences, City Hospital, Dudley Road, Birmingham B18 7QH, United Kingdom. E-mail: g.y.h.lip@bham.ac.uk.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Based on this modeling analysis of net clinical benefit, edoxaban is preferable to either warfarin or no treatment for all those with AF requiring OAC, and the effect is more marked in those at high risk of stroke.

TRANSLATIONAL OUTLOOK: In patients with AF whose risk of stroke calls for anticoagulation (i.e., $CHA_2DS_2VASc \geq 1$), 30-mg edoxaban once daily brings a NCB saving of 4.1 major events per 1,000 patients per year and a number needed to benefit of 244 compared with warfarin. This translates to a saving of more than 17,000 events in Europe annually. The edoxaban 60-mg dose has a NCB of 8.1 events, a number needed to benefit of 123 patients, translating to more than 33,000 events saved in Europe each year. In those at high risk of stroke ($CHA_2DS_2VASc \geq 2$), edoxaban 30 mg once daily brings an NCB of 5.7 events, a number needed to benefit of 175, and so a predicted saving of more than 19,000 events in Europe annually. The 60-mg dose has a NCB of 8.9 events, a number needed to benefit of 112, and so a predicted saving of more than 30,000 events in Europe annually.

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KEY WORDS **atrial fibrillation, edoxaban, net clinical benefit, oral anticoagulation, warfarin**