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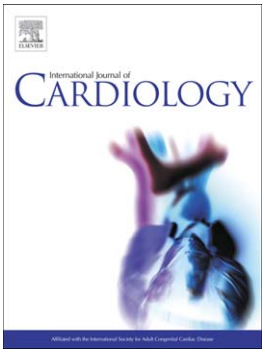

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Andrew D. Blann, Amitava Banerjee, Deirdre A. Lane, Christian Torp-Pedersen, Gregory Y.H. Lip

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Net clinical benefit of edoxaban versus no treatment in a 'real world' atrial fibrillation population: A modelling analysis based on a nationwide cohort study

Andrew D. Blann	PhD FRCPath[1]
Amitava Banerjee	MPH DPhil[1]
Deirdre A. Lane	PhD FRCPE[1]
Christian Torp-Pedersen	MD PhD[2]
Gregory Y. H. Lip	MD FRCP[1,2]

[1]University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Birmingham, B18 7QH, United Kingdom; and [2]Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark.

Address for correspondence

Professor GYH Lip: Telephone: +44 121 507 5080; Fax: +44 121 5544083;

g.y.h.lip@bham.ac.uk

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Abstract

Background In non-valvular atrial fibrillation (AF), oral anticoagulation reduces the risk of thromboembolism such as stroke and systemic embolism (SSE), but increases the risk of major bleeding such as intracranial haemorrhage (ICH). The risk-benefit balance between SSE versus ICH can be expressed as the net clinical benefit (NCB); however, the risk of SSE and ICH varies according to clinical factors that can be assessed using $CHADS_2$, CHA_2DS_2-VASc (both quantifying risk of stroke) and HAS-BLED (quantifying risk of major bleeding) scores, respectively.

Methods Using established modelling based on event rates for thromboembolism and haemorrhage in the Danish nationwide cohort study, we tested the hypothesis that edoxaban has a superior NCB compared with warfarin.

Results In our overall model, compared to no treatment, warfarin had a NCB of 0.26 (95% CI 0.24,0.28) events prevented per 100 patient years, edoxaban 60 mg daily a NCB of 0.71 [0.69,0.76], and edoxaban 30 mg daily a NCB of 0.71 [0.0.68,0.73]. When compared to no treatment, both doses of edoxaban have superior NCB values than those of warfarin at all $CHADS_2$ and CHA_2DS_2-VASc scores. At $CHADS_2$ ≥2 and CHA_2DS_2-VASc ≥2, edoxaban 60 mg dose had a better NCB than the 30 mg dose or warfarin, when compared to no treatment. With HAS-BLED score ≥3, both doses of edoxaban had a positive NCB compared to warfarin, at $CHADS_2$ or CHA_2DS_2-VASc ≥2.

Conclusion Our modelling study suggests that both 30 mg and 60 mg doses of edoxaban have a favourable NCB compared to warfarin, and the degree of benefit differs according to $CHADS_2$, CHA_2DS_2-VASc and HAS-BLED scores. At CHA_2DS_2-VASc score ≥2, both edoxaban

doses were superior to warfarin, but compared to no treatment, the 60 mg dose had a better NCB than the 30mg dose or warfarin.

Introduction

As non-valvular atrial fibrillation (AF) confers an increased risk of stroke and systemic embolism, guidelines recommend oral anticoagulation (OAC) to reduce this risk[1]. However, OAC also brings an increased risk of major bleeding, such as gastrointestinal and intracranial haemorrhage (ICH). The concept of net clinical benefit (NCB) has been used to quantify the balance between a reduced risk of stroke and systemic embolism compared to an increased risk of ICH with OAC in the setting of stroke prevention in patients with AF. Indeed, patients at highest risk of stroke and systemic embolism gain the greatest benefit from OAC[2].

The risk of stroke and systemic embolism in AF is not homogeneous, but depends upon the presence of certain clinical factors, alone or in combination. Major stroke risk factors have been combined to give the $CHADS_2$ (Chronic heart failure, Hypertension, Age >75 years, Diabetes mellitus (all 1 point), Stroke or transient ischaemic attack (2 points)) and CHA_2DS_2-VASc (Chronic heart failure, Hypertension, Age >75 years (2 points), Diabetes mellitus, Stroke, systemic embolism or transient ischaemic attack (2 points), Vascular disease, Age 65-74, Sex category i.e. female) scores[3,4]. Both scores are used to assess the risk of stroke and systemic embolism in AF, and incorporated to guidelines for risk stratification[1]. The use of OAC is also associated with bleeding (including ICH), and once more, certain risk factors have been used to develop the HAS-BLED (Hypertension, Abnormal liver/renal function, prior Stroke/thromboembolism, Bleeding tendency, Labile international normalised ratio, Elderly (e.g. age over 65 years), Drugs (e.g. concomitant use of aspirin or NSAIDs, or alcohol excess) score for bleeding risk stratification[6].

The vitamin K antagonists (VKAs, e.g. warfarin) have traditionally been the only available OAC. More recently, several non-VKA oral anticoagulants (NOACs) have shown favourable efficacy and safety results, compared with warfarin[7-10]. Of these NOACs, the oral factor Xa inhibitor edoxaban, at low and high doses of 30 mg or 60 mg (respectively) once daily, was found to be non-inferior to warfarin in protecting against stroke and systemic embolism in AF, and was associated with significantly less ICH, major bleeding and death from cardiovascular causes than warfarin[10].

Highly structured randomised controlled trials of NOACs may fail to translate to a 'real world' population, where the value of these agents also needs to be determined and compared with that of a VKA. In data from the Danish National Patient Registry on patients with AF diagnosed between 1997 and 2008[11], we demonstrated that dabigatran, rivaroxaban and apixaban would each be likely to have a favourable NCB (i.e. fewer cases of stroke and systemic embolism and fewer cases of ICH) compared to warfarin[12]. It is unclear whether or not edoxaban offers the same advantages, as each of the NOACs has different characteristics, and so any such data would be a potentially valuable addition to our management of these drugs. Using the same modelling approach, we hypothesised a superior 'real world' NCB for edoxaban with respect to warfarin, and that this benefit would vary according to the risk of stroke or systemic embolism and ICH (as defined by $CHADS_2$, CHA_2DS_2-VASc and HAS-BLED scores, respectively) on the basis of clinical trial outcome data[10].

Methods

Study population

The cohort used in this model was patients with non-valvular AF from the Danish National Patient Registry[11] who were diagnosed with AF between 1997 and 2008. AF was defined by a discharge diagnosis of AF or atrial flutter, absence of previous diagnosis of mitral or aortic valve disease, and absence of mitral or aortic valve surgery. The Danish National Patient Registry has registered all hospital admissions since 1978. At discharge each admission is coded by one primary and, if necessary one or more secondary diagnoses according to the International Classification of Diseases. The diagnosis of AF has been well-validated from Danish registries and the Patient Registry is linked to the Danish Registry of Medicinal Product Statistics (prescription registry), the National Causes of Death Registry, and the civil registration system providing a permanent and unique person registration number for all Danish citizens. Detailed history, including pharmacotherapy, and risk stratification scores for stroke and systemic embolism and major bleeding (i.e., $CHADS_2$, CHA_2DS_2-VASc and HAS-BLED) were available for all patients[3,4,6]. Published data of 96,308 patients (58,883 not treated with either an anti-platelet or with warfarin, and 37,425 patients treated with warfarin) followed up for up to 12 years with a mean of 3.83 years (= 368,860 person years) also included outcomes, including rates of ischaemic stroke, ICH, thromboembolism, cardiovascular death and acute coronary syndromes[11]. Treatment periods were determined for each patient by dividing the number of tables dispensed with the estimated daily dosage, a method described in detail previously and which allows the patient to be considered as at risk only during treatment periods[13-15]. These data were compared with those from the ENGAGE AF-TIMI 48 trial of edoxaban[10].

Model assumptions

The event rates per 100 person-years for ischaemic stroke and systemic embolism and major bleeding (ICH, gastrointestinal bleeding, bleeding from the urinary tract, etc.) were calculated using data from the Danish nationwide cohort study population for patients on no treatment with and on warfarin, stratified by stroke risk as predicted by their $CHADS_2$ and CHA_2DS_2VASc scores[11]. Using the modified intention to treat primary end points of stroke and systemic embolic event data (table 2), and the ICH data (table 3) of the ENGAGE AF study[10], the equivalent event rates were estimated for the Danish population. For this model, the 'real world' hazard ratios of the sum of stroke and systemic embolic event with edoxaban compared to warfarin were taken to be 0.79 for edoxaban 60 mg od and 1.07 for edoxaban 30 mg od. The 'real world' hazard ratios of ICH with edoxaban compared to warfarin were assumed to be 0.47 for edoxaban 60 mg od and 0.26 for edoxaban 30 mg od[10]. The relative risks of stroke, systemic embolic event and ICH were assumed to be constant across all categories of thrombosis risk and bleeding risk.

The number of patients needed to treat (NNT) to prevent one ischaemic stroke and systemic embolism per year was calculated as the reciprocal of the absolute risk reduction (i.e. 1/ARR), that is, the event rate on *no treatment* minus the event rate *on treatment*[12]. NNTs were also calculated for ICH with a negative value denoting the 'number needed to harm' (NNH)[12], that is, the number of patients treated in order to cause one ICH. The NCB of each anticoagulant compared with no treatment was calculated using the formula: (stroke and systemic embolism rate *on no treatment* minus stroke and systemic embolism rate *on anticoagulant) - 1.5 (*ICH rate *on anticoagulant* minus ICH rate on *no treatment)*[2]. The

weighting of 1.5 reflects the relative impact, in terms of death and disability, of an ICH. NNTs and NNHs are adjusted for a one-year period.

Results

Table 1 shows the event rates for stroke and systemic embolism per 100 patient years, and classified according to risk. In order to estimate the rates of stroke and systemic embolism whilst taking edoxaban, we multiplied the hazard ratios from the ENGAGE trial[10] with the rates from the Danish cohort[12]. The overall rate of stroke and systemic embolism whilst on warfarin was 0.53 [0.51,0.56] events/100 patient years[12], whilst on edoxaban 60 mg once daily the rate of 0.42 [0.40,0.44]) was well under half that of no treatment (1.0 [0.96,1.05][12] events/100 patient-years). These data translate to NNT of 212 patients with AF for warfarin and 172 for edoxaban 60 mg. The event rate for edoxaban 30 mg daily (0.57 [0.55,0.60] events/100 patient-years) and NNT of 232 patients was equivalent to that of warfarin, but was higher than that of edoxaban 60 mg. For both anticoagulants the event rates were greater with increasing $CHADS_2$ and CHA_2DS_2-VASc scores. NNTs for those on edoxaban and warfarin were lower with increasing scores.

Table 2 shows the event rates for ICH per 100 patient years, and when classified according to risk of thromboembolism. The overall rate of ICH whilst on warfarin (0.44 [0.42,0.45] events/100 patient-years) was worse than for no treatment (0.30 [0.29,0.31] events/100 patient-years)[12]. These data translate to warfarin causing one ICH per 714 patients treated in a year (i.e. a NNH of -714). In order to estimate the rates of ICH whilst taking edoxaban, we multiplied the hazard ratios for ICH from the ENGAGE trial[10] with the rates of ICH from the Danish cohort[12]. In this model, both doses of edoxaban had significantly lower adjusted

rates of ICH than that of warfarin and no treatment (edoxaban 30 mg 0.11 [0.11,0.12] events/100 patient-years, NNT 526; edoxaban 60 mg 0.21 [0.20,0.21] events/100 patient-years, NNT 1,111) and the rate of ICH of 30 mg dose of edoxaban was superior to that of the 60 mg dose. As with stroke and systemic embolism, for both anticoagulants, the event rates were greater with increasing $CHADS_2$ and CHA_2DS_2-VASc scores whilst the NNTs fell with increasing scores, except for warfarin and $CHADS_2$ score.

NCB of warfarin and edoxaban when compared with no treatment

Table 3 presents the NCB of warfarin and edoxaban when compared with no treatment. Warfarin use is associated with a reduced rate of stoke and systemic embolism (Table 1) but an increased rate of ICH (Table 2) compared with no treatment. For any AF patient requiring OAC, the NCB is 0.26 [0.24,0.28] events prevented/100 patient-years if treated with warfarin. Similarly, the NCB for edoxaban 30 mg is 0.71 [0.68,0.73] events prevented, and for edoxaban 60 mg, 0.71 [0.69,0.76] events prevented.

In considering risk profiles with the $CHADS_2$ and CHA_2DS_2-VASc scores, differences emerge. At all $CHADS_2$ scores, and CHA_2DS_2-VASc score 2-9, warfarin has a positive NCB compared to no treatment, but at CHA_2DS_2-VASc scores 0 and 1, warfarin has no positive benefit over no treatment. At all $CHADS_2$ and CHA_2DS_2-VASc scores, both doses of edoxaban have superior NCB values than no treatment. At $CHADS_2$ scores 0 and 1, the two edoxaban doses bring similar NCBs compared to each other, and are superior to no treatment [Table 3], but at $CHADS_2$ 2-6, the 60 mg dose had a better NCB than the 30mg dose or warfarin. At CHA_2DS_2-VASc scores 0 and 1, both doses of edoxaban had marginally positive NCBs compared to no treatment, but the 30mg dose had superior NCBs than the 60 mg dose. At CHA_2DS_2-VASc

score 2-9, the 60 mg dose had a better NCB than the 30 mg dose or warfarin. For both OACs, NCBs increased with increasing $CHADS_2$ and CHA_2DS_2-VASc scores.

NCB for edoxaban 30 mg and 60 mg compared with warfarin

Table 4 shows the NCB for edoxaban 30 mg and 60 mg compared with warfarin, according to $CHADS_2$, CHA_2DS_2-VASc and HAS-BLED scores. At low bleeding risk (HAS-BLED score ≤ 2), both edoxaban doses had superior NCB to warfarin regardless of $CHADS_2$ or CHA_2DS_2-VASc score. At a high risk of bleeding (HAS-BLED score ≥3), and at $CHADS_2$ 0 and CHA_2DS_2-VASc score 1, neither dose of edoxaban had superior NCB to warfarin and the two edoxaban doses had similar NCBs. At all other $CHADS_2$ and CHA_2DS_2-VASc scores, both doses of edoxaban had superior NCBs than warfarin, and was similar for the two edoxaban doses. These results are illustrated in figure 1.

Sensitivity analysis

We performed a further analysis based on the likelihood that the rate of ICH were twice that observed in the trial, and that the rate of stroke and systemic embolism were lowered by 50%. Results presented in supplementary table 1 indicate that outcome would not be the same, with in some cases the NCB of warfarin would become not significant, whereas all cases of the use of edoxaban would still be significant, except that for patients with CHA_2DS_2VASc 1, edoxaban 30mg od would provide no clear NCB advantage. This translates, in supplementary table 2, to no changes in the extent to which either doses of edoxaban are or are not preferable to warfarin.

Discussion

In this modelling analysis, we have shown that the NCBs and NNTs of the 30 mg and 60 mg doses of edoxaban, with respect to warfarin, are favourable but differ according to $CHADS_2$, CHA_2DS_2-VASc and HAS-BLED scores. At high stroke risk (i.e. CHA_2DS_2-VASc score ≥2), both edoxaban doses were superior to warfarin, but compared to no treatment, the 60 mg dose had a better NCB than the 30mg dose or warfarin. With high bleeding risk (HAS-BLED ≥3), both doses of edoxaban had a positive NCB compared to warfarin, at $CHADS_2$ or CHA_2DS_2-VASc scores ≥2.

When using an OAC in AF patients, the benefit of a reduction in the risk of a thrombotic event such as stroke and systemic embolisation must be weighed against the risk of major bleeding such as ICH. However, the risk of stroke and thromboembolism in an individual varies markedly according to the sum of certain risk factors. As we previously reported[11,12], the NCB is only negative with warfarin at a CHA_2DS_2-VASc score 0 or 1, reflecting the 'truly low risk' status of these patients. In our model for the present study, without risk factor stratification, both doses of edoxaban are predicted to result in lower rates of both types of events (thrombotic and haemorrhagic, and so equivalent NCBs) compared with warfarin. Our prediction that a NOAC brings a reduction of over 50% in the risk of ICH in a real world database is entirely in line with a recent meta-analysis[16]. However, these data assume each risk regardless of concurrent clinical and demographic features.

Classifying stroke risk by the $CHADS_2$ method, at low and moderate risk of stroke, both doses of edoxaban provide similar improved NCB over warfarin. At the high risk of stroke, high-dose (60 mg) edoxaban is superior to both low dose (30 mg) edoxaban and warfarin.

The CHA_2DS_2-VASc system recognises a limitation inherent in $CHADS_2$, in that the latter places more patients at low risk of stroke than the former, potentially denying treatment to some[4]. This is borne out by data indicating that at low CHA_2DS_2-VASc scores of 0 and 1, when compared to no treatment, warfarin causes more harm than good whereas at a $CHADS_2$ score of 0, the use of warfarin can be justified in some patients. At a low and moderate CHA_2DS_2-VASc risk of stroke (scores 0 and 1), edoxaban 30 mg provides more benefit than edoxaban 60 mg, whereas at high risk (CHA_2DS_2-VASc score 2-9), edoxaban 60 mg is preferred.

Practitioners and patients alike fear haemorrhage, the risk of which can be determined by the HAS-BLED score[5]. When risk of bleeding is low (HAS-BLED score $\leq$2), our modelling data predict that edoxaban 30 mg is the preferred dose regardless of stroke risk, except when defined by $CHADS_2$ 2-6, where the two doses bring equivalent benefit. Patients with a high HAS-BLED score (≥3), and a low risk of stroke according to $CHADS_2$ (score 1) or a moderate risk of stroke according CHA_2DS_2-VASc (score 1) will benefit equally from any oral anticoagulant. Due to low numbers of patients and events, our analyses of CHA_2DS_2VASc score 0 and high bleeding risk may be unreliable. Patients at high risk of stroke according to $CHADS_2$ score 2-6 or CHA_2DS_2VASc score 2-9 gain the same benefit from either dose of edoxaban. The NCB data are broadly comparable with those of other NOACs, which have NCBs between 0.58 and 3.76 events prevented/100 patient-years[12].

Limitations

We note several limitations of this analysis. Our model calls for merging of data from a formal clinical trial[10] with that from a community population[11], two groups who may differ in clinical profiles. Indeed, we assume the relative risk observed in a RCT would be similar to

the one happening in the real-world population, which may be an oversimplification; indeed, patients in RCTs are generally not representative of the general population and therefore, the risks that are observed in RCTs cannot be assumed to be the same in the 'real world' population. In addition, other models have been used, so results may be different. Accordingly, there may be error in the estimates of the effects of edoxaban compared to warfarin. The mean (standard deviation) $CHADS_2$ score in the ENGAGE AF-TIMI 48 trial was 2.8 (1.0)[10], that for the Danish cohort[11] is estimated to be perhaps 1.25 (0.8), indicating that the latter are at considerably less risk of stroke. Furthermore, we cannot determine the degree of warfarin anticoagulation control in the two groups and assume they are equal: it is possible that INR control is less rigorous in the community and this may impact on outcomes [17,18]. Furthermore, since warfarin doses vary frequently, we acknowledge the limitation that this is difficult to extrapolate daily dosage and thus drug coverage based on administrative data. The equation of Singer et al[2] balances risk of ischaemic stroke and systemic emboli with those of any ICH, and did not include a sudden neurological deficit lasting less than 24 hours (i.e. a transient ischaemic attack (TIA). Olesen et al[11] defined thromboembolism as peripheral artery embolism, TIA and ischaemic stroke, and bleeding as gastrointestinal, urinary tract and airways as well as intracranial. These differences may also lead to error. Statistical differences at $p<0.05$ are assumed if 95% confidence intervals fail to overlap, but these intervals are defined by power in terms of number of events and number of patients (in the Danish cohort[11], 38,546 patients had a HAS-BLED score $\geq$3, whereas 93,826 (2.4x more) had a HAS-BLED score $\leq$2). This may explain why, at a $CHADS_2$ score of 0, a 56% better NCB for edoxaban 30 mg at HAS-BLED score $\geq$3 compared to edoxaban 60 mg is not significant (table 4), whereas a smaller 31% at $CHADS_2$ score of 1 and 26% at CHA_2DS_2VASc score of 2-9 of the respective better NCB for the 30 mg dose at HAS-BLED

score ≥2 is statistically significant. Accordingly, we note the caveat that wide (and so overlapping) confident intervals consequent to low power may give rise to false negatives. Finally, we note that Danish cohort was studied between 1997 and 2008, whilst the ENGAGE-AF trial was conducted between 2008 and 2010. Accordingly, differences in general clinical practice and different drugs and other treatments over more than a decade may also lead to error or residual confounding. A further limitation is that the results from the Engage AF-TIMI 48 trial of edoxaban[10] may not reflect the real world, and that one might expect that the risk of ICH would be greater. In addressing this point our sensitivity analysis based on the likelihood that the rate of ICH were twice that observed in the trial, and that the rate of stroke and systemic embolism were lowered by 50% translated, to no profound changes in the extent to which either doses of edoxaban are or are not preferable to warfarin.

In conclusion, based on this modelling analysis of NCB, edoxaban is preferable over warfarin for 'all comers' with AF, with the two edoxaban doses apparently bringing the same favourable NCB compared to warfarin. However, degree of benefit differs according to $CHADS_2$, CHA_2DS_2-VASc and HAS-BLED scores. At CHA_2DS_2-VASc score ≥2, both edoxaban doses were superior to warfarin, but compared to no treatment, the 60 mg dose had a better NCB than the 30mg dose or warfarin. Assessment of the patient's risk profile may allow a more tailored and efficient approach to stroke prevention.

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GL provided the idea for the article and contributed to drafting and subsequent revisions. ADB performed the analyses and contributed to manuscript revisions. AB, DAL and CTP contributed to analyses and revisions of the manuscript. Funding – Supported by Daiichi Sankyo.

Competing interests

Dr. Blann has received funding for research from Boehringer Ingelheim, and been on the speaker bureau for Bayer, BMS/Pfizer and Boehringer Ingelheim. Prof. Lip has served as a consultant for Bayer, Astellas, Merck, AstraZeneca, Sanofi, BMS/Pfizer and Boehringer Ingelheim and has been on the speakers bureau for Bayer, BMS/Pfizer, Boehringer Ingelheim, Roche and Sanofi. Dr. Banerjee and Dr Torp-Pedersen have no conflicts to declare. Dr. Lane has received investigator initiated educational grants from Bayer Healthcare and Boehringer Ingelheim and has been on the speaker bureau for Boehringer Ingelheim, Bayer, and BMS/ Pfizer, and is a member of the AEGEAN Steering committee.

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Table 1: Event rates (95% confidence interval) modelled for stroke and systemic embolism per 100 patient years in a real world cohort adjusted for effect size for no treatment, warfarin, or 30 mg or 60 mg dose of edoxaban.

	No Treatment	Warfarin (dose adjusted)	NNT	Edoxaban (30 mg)	NNT	Edoxaban (60 mg)	NNT
All subjects	1.00 (0.96,1.05)	0.53 (0.51,0.56)	212	0.57 (0.55,0.60)	232	0.42 (0.40,0.44)	172
$CHADS_2$ score							
0	0.20 (0.18,0.22)	0.10 (0.09,0.11)	1000	0.11 (0.10,0.12)	1111	0.08 (0.07,0.09)	833
1	1.00 (0.92,1.09)	0.50 (0.46,0.55)	200	0.53 (0.49,0.59)	213	0.39 (0.36,0.43)	164
2-6	3.01 (2.85,3.16)	1.65 (1.56,1.74)	74	1.76 (1.67,1.86)	80	1.30 (1.23,1.38)	58
CHA_2DS_2-VASc score							
0	0.07 (0.06,0.09)	0.04 (0.03,0.05)	3333	0.04 (0.03,0.05)	3703	0.03 (0.02,0.05)	2500
1	0.10 (0.09,0.12)	0.05 (0.04,0.06)	2000	0.05 (0.04,0.06)	2128	0.04 (0.03,0.05)	1667
2-9	2.00 (1.91,2.10)	1.08 (1.02,1.12)	109	1.16 (1.09,1.22)	119	0.85 (0.81,0.88)	87

NNT (number needed to treat): number of patients needed to treat to prevent one ischaemic stroke or systemic embolism per year. NNT is calculated as 1/ARR, where ARR is the absolute risk reduction, i.e. event rate on no treatment-event rate on treatment.

Table 2: Event rates (95% confidence interval) modelled for intra-cranial haemorrhage per 100 patient years in a 'real world cohort' taking 30 mg or 60 mg dose of edoxaban adjusted for effect size for no treatment and warfarin.

	No Treatment*	Warfarin (dose adjusted)*	NNH	Edoxaban (30 mg)	NNT	Edoxaban (60 mg)	NNT
All subjects	0.30 (0.29,0.31)	0.44 (0.42,0.45)	714	0.11 (0.11,0.12)	526	0.21 (0.20,0.21)	1,111
$CHADS_2$ score							
0	0.10 (0.09,0.11)	0.15 (0.14,0.17)	2000	0.04 (0.04,0.04)	1667	0.07 (0.07,0.08)	3,333
1	0.30 (0.28,0.32)	0.39 (0.37,0.42)	1111	0.10 (0.10,0.11)	500	0.18 (0.17,0.20)	833
2-6	0.40 (0.38,0.42)	0.44 (0.41,0.46)	2500	0.11 (0.11,0.12)	345	0.21 (0.19,0.22)	526
CHA_2DS_2-VASc score							
0	0.05 (0.04,0.06)	0.09 (0.08,0.11)	2500	0.02 (0.02,0.03)	3,333	0.04 (0.04,0.05)	10,000
1	0.10 (0.09,0.11)	0.14 (0.13,0.16)	2500	0.04 (0.03,0.04)	1,667	0.07 (0.06,0.08)	3,333
2-9	0.30 (0.29,0.31)	0.36 (0.34,0.37)	1667	0.09 (0.09,0.10)	476	0.17 (0.16,0.17)	769

NNT: number of patients needed to treat to prevent one ICH per year. NNH = number needed to harm, i.e. the number of patients needed to treat to cause an ICH. NNT and NNH are calculated as 1/ARR, where ARR is the absolute risk reduction, i.e. event rate on no treatment-event rate on treatment. *Data from reference 11.

Table 3: Net clinical benefit (95% confidence interval) of warfarin and 30 mg and 60 mg doses of edoxaban compared to no treatment.

	Warfarin (dose adjusted)	Edoxaban (30 mg)	Edoxaban (60 mg)
All subjects	0.26 (0.24,0.28)	0.71 (0.68,0.73)	0.71 (0.69,0.76)
$CHADS_2$ score			
0	0.02 (0.01,0.03)	0.18 (0.15,0.20)	0.16 (0.14,0.17)
1	0.36 (0.32,0.39)	0.77 (0.70,0.81)	0.79 (0.72,0.84)
2-6	1.3 (1.2,1.4)	1.68 (1.58,1.75)	1.99 (1.90,2.08)
CHA_2DS_2-VASc score			
0	-0.03 (-0.03, -0.035)	0.07 (0.06,0.08)	0.05 (0.04,0.05)
1	-0.01 (-0.01, -0.015)	0.14 (0.14,0.16)	0.10 (0.10,0.11)
2-9	0.83 (0.81,0.89)	1.15 (1.12,1.19)	1.34 (1.29,1.43)

Net clinical benefit (NCB)[Events prevented per 100 person-years (95% confidence interval)] is calculated as annualised (stroke and systemic embolism rate $_{\text{off treatment}}$ – stroke and systemic embolism rate $_{\text{on treatment}}$) - 1.5 x (ICH rate $_{\text{on treatment}}$ – ICH rate $_{\text{off treatment}}$)^2.

Table 4: Net clinical benefit (95% confidence interval) of 30 mg and 60 mg doses of edoxaban versus warfarin on the risk of stroke, systemic embolism and ICH risk as assessed by the $CHADS_2$, CHA_2DS_2-VASc and HAS-BLED scores.

	HAS-BLED Score ≤2		HAS-BLED Score ≥3	
	Edoxaban (30 mg)	**Edoxaban (60 mg)**	**Edoxaban (30 mg)**	**Edoxaban (60 mg)**
$CHADS_2$				
0	1.80 (1.59,2.05)	1.16 (1.01,1.34)	1.20 (-0.74,3.36)	0.77 (-0.99,2.64)
1	2.34 (2.10,2.61)	1.78 (1.58,2.01)	1.96 (1.34,2.60)	1.44 (0.91,1.98)
2-6	3.29 (2.94,3.64)	2.77 (2.46,3.09)	3.84 (3.40,4.30)	3.36 (2.96,3.78)
CHA_2DS_2-VASc				
0	2.06 (1.65,2.49)	1.30 (1.00,1.58)	-	-
1	1.65 (1.34,1.97)	1.05 (0.81,1.29)	1.21 (-0.25,2.89)	0.82 (-0.48,2.19)
2-9	2.63 (2.42,2.84)	2.09 (1.91,2.26)	3.43 (3.07,3.80)	2.94 (2.61,3.28)

Net clinical benefit (NCB) = events prevented per 100 patient-years (95% confidence interval) of edoxaban is calculated as annualised NCB on warfarin[12] - [1-relative risk of stroke and systemic embolism for edoxaban[10] x stroke and systemic embolism rate on warfarin[11]]+[1.5x (1-relative risk for ICH on edoxaban[10] x rate of ICH on warfarin[11])], modified from Singer et al[2] .

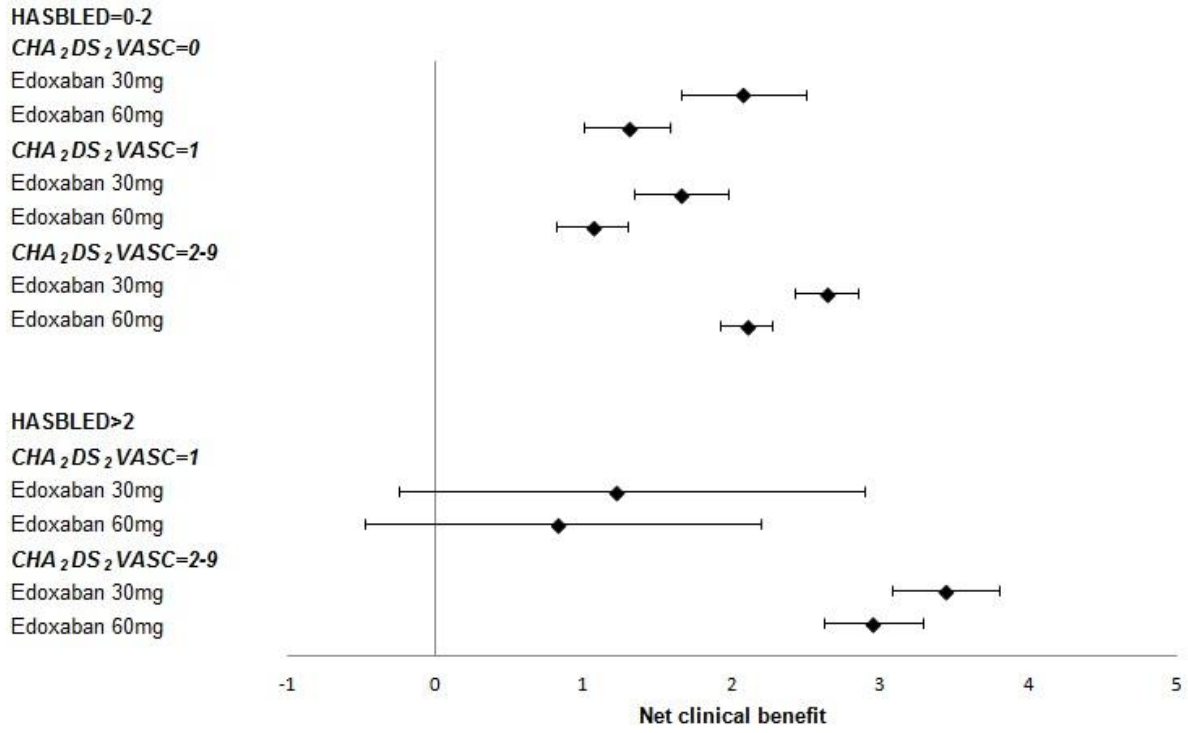

Fig. 1