Edoxaban versus placebo, aspirin, or aspirin plus clopidogrel for stroke prevention in atrial fibrillation
An indirect comparison analysis
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Summary
As non-valvular atrial fibrillation (AF) brings a risk of stroke, oral anticoagulants (OAC) are recommended. In ‘real world’ clinical practice, many patients (who may be, or perceived to be, intolerant of OACs) are either untreated or are treated with anti-platelet agents. We hypothesised that edoxaban has a better net clinical benefit (NCB) (balancing the reduction in stroke risk vs increased risk of haemorrhage) than no treatment or anti-platelet agents. We performed a network meta-analysis of published data from 24 studies of 203,394 AF patients to indirectly compare edoxaban with aspirin alone, aspirin plus clopidogrel, and placebo. Edoxaban 30 mg once daily significantly reduced the risk of all stroke, ischaemic stroke and mortality compared to placebo and aspirin. Compared to aspirin plus clopidogrel, there was a lower risk of intra-cranial haemorrhage (ICH). Edoxaban 60 mg once-daily had a reduced risk of any stroke and systemic embolism compared to placebo, aspirin, and aspirin plus clopidogrel. Mortality rates for both edoxaban doses were estimated to be lower compared to any anti-platelet, and significantly lower compared to placebo. With overall reduced risk of ischemic stroke and ICH, both edoxaban doses bring a NCB of mean (SD) 1.68 (0.15) saved events per 100 patients per year compared to anti-platelet drugs in a clinical trial population. The NCB was demonstrated to be lower, at 0.77 (0.12) events saved (p<0.01) when modeled to data from a ‘real world’ cohort of AF patients. In conclusion, edoxaban is likely to provide even better protection from stroke and ICH than placebo, aspirin alone, or aspirin plus clopidogrel in both clinical trial populations and unselected community populations. Both edoxaban doses would also bring a positive NCB compared to anti-platelet drugs or placebo/non-treatment based on ‘real world’ data.

Keywords
Oral anti-coagulation, atrial fibrillation, edoxaban, warfarin, aspirin, clopidogrel

Introduction
Patients with non-valvular atrial fibrillation (AF) are at risk of stroke and systemic embolism, and oral anticoagulants (OAC) are recommended accordingly, whether vitamin-K antagonists (VKAs) or Non-VKA Oral Anti-Coagulants (NOACs) (1). The numerous disadvantages of VKAs, which include an increased risk of gastro-intestinal and intracranial haemorrhage (ICH), and many food and drug interactions, have prompted some practitioners to offer alternatives such as anti-platelet therapy, or even (for those, such as the elderly, considered to be at the highest risk of haemorrhage) no treatment (2–4). Many, if not all, of these problems could be abolished with the use of a NOAC, which overall have better relative efficacy and safety profile (e.g. in terms of reduced risk of ICH) than VKAs (5–7). The effectiveness and safety of the NOAC edoxaban was examined in the ENGAGE AF trial, a randomised, double-blind study comparing the two once-daily doses of edoxaban with dose-adjusted warfarin in AF patients with moderate-to-high-risk of stroke over a median follow-up period of 2.8 years (7). Both edoxaban doses were non-inferior to warfarin in the prevention of stroke or systemic embolism with significantly lower rates of bleeding and cardiovascular death, but it is unknown how they compare to the non-VKA strategies of anti-platelet or no therapy.

Although there are no direct head-to-head clinical trials of edoxaban versus anti-platelet or no therapy (and none are likely to be undertaken for edoxaban), there are models for calculating the indirect comparisons of different treatments. These are several indirect...
methods, which include those of Bucher et al., meta-analysis, and network meta-analysis (8–10), that have been used in several studies to compare VKAs with NOACs, reinforcing the broad view (5, 6, 11–13) that NOACs are at least as effective at reducing the risk of stroke and systemic embolism as are VKAs (and in several cases are more effective), and have improved safety profiles in terms of fewer cases of ICH and major bleeding. Such indirect methods have previously been used to compare other NOACs (13, 14) as well as comparing NOACs with placebo and the use of anti-platelets (11). The indirect comparison of Skjøth et al. (15) indicated that the lower dose regimen of edoxaban was less efficacious than dabigatran 150 mg and rivaroxaban, but associated with less major bleeding, whereas higher dose regimen edoxaban was comparable to apixaban, dabigatran 110 mg twice daily and rivaroxaban in terms of efficacy. Cameron et al. (12) showed that aspirin and aspirin with clopidogrel are associated with an increased risk of major bleeding and of stroke or systemic embolism than either dose of edoxaban. Verdecca et al. (16) showed that both dosing regimens of edoxaban are associated with a reduced risk of all stroke and all-cause mortality compared to putative placebo. Doglotti et al. (17) concluded that of placebo, anti-platelets, dabigatran, rivaroxaban and apixaban, the use of dabigatran 150 mg was associated with lowest risk of stroke or systemic embolisation, and that aspirin plus clopidogrel was associated with the highest risk of major bleeding.

The objectives of the present study were to use the network meta-analysis approach to determine whether or not once daily edoxaban 30 mg and 60 mg provides better protection from all stroke, ischaemic stroke, systemic embolism, mortality, intracranial haemorrhage and acute myocardial infarction than do aspirin (alone or with clopidogrel) or placebo in clinical trial populations and in ‘real world’ unselected general populations. An analysis of VKA as a comparator is included to provide perspective.

Methods

Our methods are described elsewhere (13–16). Briefly, a systematic literature review was conducted in the Cochrane database, MEDLINE and MEDLINE In-process, EMBASE and BIOSIS to identify randomised controlled trials of OACs (any VKA or edoxaban) and anti-platelets (aspirin or aspirin plus clopidogrel) for the prevention of stroke in AF. Exclusion criteria were non-AF studies, phase 1 studies, non-randomised studies, short-term phase 2 studies, single arm studies, study reviews, letters and comment articles. The Jadad scale (18) was used to assess the quality of clinical trials: those scoring 2 or less were excluded.

Common outcomes between these studies were all forms of stroke, ischaemic stroke, systemic embolism, mortality, ICH and acute myocardial infarction. Outcomes and events such as transient ischaemic attack, gastrointestinal bleeding, minor bleeds and any bleeds were excluded due to lack of formal definition. Other end points and analyses (such as pulmonary embolism vs deep-vein thrombosis) were excluded because of small numbers and risk of false positive/false negative. Trial data on number of events and trial participants were collected if the endpoint was reported (i.e. at least 0, but not missing). Relative risks of edoxaban compared to the alternatives (placebo, anti-platelets and adjusted-dose VKA) were estimated in a multivariate network meta-analysis (19) accounting for multi-arm trials. Some endpoints were only reported with very few or no reported events in some of the smaller trials, this may lead to estimation problems due to relative risks equal or close to zero. To overcome this, a Yates continuity correction was applied by adding 0.5 to events and sample size (20). Results are presented as relative risk with 95% confidence intervals (95% CIs).

Net clinical benefit (NCB) was calculated by a modification of Singer’s method (21), designed to balance the saving in thrombosis with the increase in bleeding due to warfarin in terms of risk differences. Singer et al. (21) suggested weighing the increase in bleeding by a factor between 1.5 and 2. In this study the weight 1.5 was used. The net clinical benefit therefore depends on the rates \((R)\) of ischaemic stroke \((R_{stroke})\) and ICH \((R_{bleeding})\), and relative risk \((RR)\) in the hypothetical population in which edoxaban and the alternatives are assumed applied. Based on the estimated relative risks the net clinical benefits was obtained as \(N CB = R_{stroke} \times (1 - R_{stroke, edoxaban vs alternative}) - 1.5 \times R_{bleeding} \times (R_{bleeding, edoxaban vs alternative} - 1)\). Approximate 95% CIs were calculated as \(N CB \pm 1.96 \times Var(N CB)\), where the variance \(Var(N CB) = R_{stroke}^2 \times Var(R_{stroke, edoxaban vs alternative}) + (1.5 \times R_{bleeding})^2 \times Var(R_{bleeding, edoxaban vs alternative})\).

The variances of the relative risk, \(Var(R)\) were approximated from the estimated confidence intervals: \(Var(R) = [(R_{upper} - R_{lower})^2 / (2 \times 1.96)^2]\). Positive net clinic benefit indicates benefit for edoxaban. Numbers needed to treat per 100 patient years were calculated as the reciprocal of the difference in risks between the treatments (11), i.e. \(N N T = 100 / [R_{stroke} (1 - R_{stroke, edoxaban vs alternative}) + (1.5 \times R_{bleeding})]\) with positive numbers in benefit for edoxaban. The NCB depend on the endpoint rates in the population, we derived these from two sources: all non-placebo arms in the included randomised trials \(R_{stroke} = 2.89\%\), \(R_{bleeding} = 0.85\%\), see Suppl. Table 1, available online at www.thrombosis-online.com, and from an unsselected non-clinical trial (real world) Danish nationwide cohort study (23) \(R_{stroke} = 1.42\%, R_{bleeding} = 0.27\%\) based on 7,210 and 1,381 reported events on ischaemic stroke and ICH, respectively. The net clinical benefit aspect is thereby reported for trial population and for a real-world cohort with a lower risk in comparison. Further, as trial information on ICH is indeed very limited, we included real world data (23) on this endpoint on warfarin respectively non-treated patients for the NCB analysis. This enabled us to reduce uncertainty of the net clinical benefit aspect to that of dose-adjusted VKA and placebo compared to the two dosing regimens of edoxaban.

StataSE v. 13.1 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX, USA: StataCorp LP) was used for the analyses.

Results

Data were obtained from 1,486 titles from 23 eligible trials with 31 direct comparisons including 71,022 patients, and a community study of 132,372 patients (23). Data were extracted for the end
Relative risks for edoxaban 30 mg once daily compared with placebo or other treatments

Edoxaban 30 mg was superior to placebo in protecting against all stroke, ischaemic stroke and mortality, and non-significantly different in all other outcomes (Figure 2). Edoxaban 30 mg was superior to aspirin alone in protecting against all strokes and ischaemic stroke, systemic embolism, mortality and non-significantly different in ICH and myocardial infarction. Edoxaban 30 mg was superior to aspirin plus clopidogrel in preventing systemic embolism and ICH and non-significantly different in all other outcomes. Edoxaban 30 mg was superior to adjusted-dose VKA in preventing ICH and mortality, and non-significantly different in all other outcomes, except ischaemic stroke, where VKA was superior, reflecting trial data (7).

Relative risks for edoxaban 60 mg once daily compared with placebo or other treatments

Edoxaban 60 mg was superior to placebo in preventing any stroke, ischaemic stroke, systemic embolism and death, and non-significantly different for ICH or acute myocardial infarction (Figure 3). Edoxaban 60 mg was superior to aspirin monotherapy and aspirin plus clopidogrel in preventing any stroke, ischaemic stroke or systemic embolism, and non-significantly different for all other outcomes. Edoxaban 60 mg was superior to adjusted-dose VKA in preventing ICH, and was non-significantly different in all other outcomes. There were no cases where edoxaban 60 mg was inferior to any other treatment modality, including dose-adjusted VKA, the latter reflecting trial data (7).

Number needed to treat estimates

The number of patients needed to treat to prevent one event whilst on edoxaban dosing regimens 30 mg or 60 mg, respectively, compared with each of the comparators, ×100 are given in Figure 2 and Figure 3, with population rates based on trial data. All but one comparison of edoxaban 30 mg with placebo or an anti-platelet resulted in a positive number needed to treat, the exception being that of dual anti-platelets preventing myocardial infarction. Similarly, all but two comparisons of edoxaban 60 mg with placebo or an anti-platelet resulted in a positive number needed to treat, the exceptions being those of placebo and aspirin alone in preventing ICH. The most efficacious uses of either dose of edoxaban were in preventing any stroke or death compared to placebo or aspirin.

Net clinical benefit (NCB)

If confined only to clinical trial data, edoxaban 30 mg compared to placebo was estimated to bring a NCB of 1.55 (95% confidence
interval –0.81 to 3.91) major events saved in 100 patient years in a trial population and 0.72 (-0.09 to 1.52) in a population cohort, whilst higher dose edoxaban 60 mg was estimated to bring a NCB of 1.52 (-1.81 to 4.84) in a trial population and 0.79 (-0.29 to 1.87) in a population cohort. A weakness of this approach is that the very small number of endpoints (and few trials per se) with a placebo arm that will inevitably result in wide confidence intervals and increase the risk of false negative.

The Danish observational cohort data from 132,372 subjects (23) brings considerably more power. Thus, adding information from this cohort on ICH risk, edoxaban 30 mg compared to placebo/non-treated was estimated to bring a net clinical benefit of 2.06 (1.30 to 2.82) in a trial population and 0.88 (0.51 to 1.15) in the population cohort. Similarly, edoxaban 60 mg was estimated to bring a net clinical benefit of 2.28 (1.70 to 2.86) in a trial population and 1.03 (0.76 to 1.30) in a population cohort.

Data on comparing edoxaban with anti-platelets and VKAs are shown in Table 1, with population rates based on clinical trial data and on observational cohort data, respectively (22, 23). In the clinical trial group and the population cohort group, both regimens of edoxaban are estimated to have positive NCB vs aspirin or aspirin plus clopidogrel. In combining the anti-platelet regimes data, any dose of edoxaban resulted in a mean (SD) NCB increase of 1.68 (0.15) major events saved in the clinical trial group. However, this effect was not as strong in the population cohort at 0.77 (0.12) major events saved (p< 0.01, paired t-test).

In the clinical trial group, although the net clinical benefit of lower dose edoxaban 30 mg compared to dose-adjusted VKA was non-significant, edoxaban 60 mg had a significant positive NCB,
Figure 3: Relative risk of outcome and number needed to treat with edoxaban 60 mg OD compared to alternatives. VKA = vitamin K antagonist. CI = confidence interval. NNT = number needed to treat, negative values translate to number needed to harm. R = risk assumed for NNT calculation. OD = once daily.

reflecting ENGAGE AF TIMI 48 trial data (7). In the population cohort group, both dosing regimens of edoxaban brought a positive but not significantly better net clinical benefit than did dose-adjusted VKA.

Discussion

In this network meta-analysis, we show that edoxaban is likely to provide equivalent or better protection from stroke and ICH than placebo, aspirin alone or aspirin plus clopidogrel in both clinical trial populations and unselected community populations. The dosing regimen of edoxaban 30 mg is estimated to provide statistically significant reductions in risk of any stroke compared to placebo and aspirin monotherapy, 54% and 40%, respectively, a reduction in the risk of death by 36% and 18% compared to placebo and aspirin, and with a non-significantly lower risk of ICH. Generally, edoxaban 30 mg was not associated with a statistically significant higher risk of any other outcomes compared with any other treatment, except for ischaemic stroke compared to dose-adjusted VKA. Although differing in some relative risk and confidence intervals, our estimates on the dose-adjusted VKA broadly mirror those of the ENGAGE AF-TIMI 48 trial (7).

Similarly, edoxaban 60 mg is estimated to provide statistically significant reductions in risk by 64%, 54% and 38% for any stroke compared to placebo, aspirin alone or aspirin plus clopidogrel, respectively. It provides an estimated 61% protection from ischaemic stroke and 33% protection from death compared to placebo, and 54% reduction in the risk of ICH compared to dose-adjusted VKA. Edoxaban 60 mg also provided 76%, 79% and 79%
In ‘real world’ clinical practice, many patients (who may be, or perceived to be, intolerant of oral anticoagulants) are either untreated or are treated with anti-platelet agents.

What is known about this topic?
- In ‘real world’ clinical practice, many patients (who may be, or perceived to be, intolerant of oral anticoagulants) are either untreated or are treated with anti-platelet agents.

What does this paper add?
- Edoxaban 30 mg once daily reduces the risk of all stroke, ischaemic stroke and mortality compared to placebo and aspirin, based on indirect comparison analyses.
- Edoxaban 60 mg once daily reduces the risk of any stroke and systemic embolism compared to placebo, aspirin, and aspirin plus clopidogrel, based on indirect comparison analyses.
- Mortality rates for both edoxaban doses were estimated to be lower compared to any anti-platelet, and significantly lower compared to placebo.
- Edoxaban is likely to provide as good or even better protection from stroke and intracranial haemorrhage than placebo, aspirin alone, or aspirin plus clopidogrel. Both edoxaban doses would also bring a positive net clinical benefit compared to anti-platelet drugs or placebo/non-treatment based on ‘real world’ data.

Adjusted-dose VKA and other NOACs are recommended in guideline for stroke prevention in AF (1–3, 25). Despite these positive data, uptake of the medications according to prevailing guidelines is poor at best (4), one study reporting that only 36% of AF patients admitted to hospital with stroke were taking an anticoagulant prior to admission, and that 38% were taking an anti-platelet drug (26). Recent data from Europe indicates that although 95.2% of AF patients are taking an anti-thrombotic therapy, 30.7% are taking aspirin and 9.9% are taking clopidogrel (27). The reasons for failure to prescribe OACs are complex, but may include lack of awareness of the ineffective nature of anti-thrombotics and/or fear of potentially fatal haemorrhage on OACs (28). Our data further supports the use of OAC over anti-platelet therapy in general and show that edoxaban 60 mg is superior to anti-platelet drugs or no treatment in reducing the risk of any stroke. Although edoxaban 60 mg is as effective in preventing stroke as is adjusted-dose VKA, it is associated with markedly fewer cases of ICH.

A weakness of clinical trial data is that it invariably fails to reflect the ‘real world’. We addressed this issue by including results from the Danish nationwide cohort study (23). In all comparisons, the NCB of edoxaban was still positive, but NCBs were lower in the real-world cohort than in the trial group, reflecting lower event rates in a general population (as the Danish nationwide cohort) compared to the cohort of patients recruited to trials.

We note several limitations, such as differences in inclusion and exclusion criteria, in study populations and in definitions of outcomes (such as ICH) in the trials that are a persistent source of heterogeneity. However, these caveats apply to all meta-analyses (5, 6, 11–17), and interpretation of results must be considered with these in mind. Available placebo trials in AF are very limited and those included in this study were all fairly small-scaled with 200–330 participants in the placebo arm. Only one study (AC-TIVE) compared dose-adjusted VKA with aspirin and aspirin plus clopidogrel (Figure 1). Consequently, few events are seen for rare endpoints as ICH leading to very wide confidence intervals with the potential for false negatives, and for this reason we used data from a large community study with many end points and thereby good power (23). The estimated relative risks and net clinical benefits of edoxaban compared to placebo are therefore to be interpreted with caution. Nevertheless, we believe our results are robust and that it provides additional evidence that edoxaban is a markedly better treatment option for preventing stroke in AF than antiplatelet drugs or no treatment. Finally, we have added

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**Table 1: Net clinical benefit with 95% CI of the number of ischaemic strokes and intracranial haemorrhages prevented by edoxaban compared to anti-platelet or dose adjusted VKA per 100 patients.**

<table>
<thead>
<tr>
<th>Comparator</th>
<th>Edoxaban 30 mg OD</th>
<th>Edoxaban 60 mg OD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial rates*</td>
<td>Cohort rates†</td>
<td>Trial rates*</td>
</tr>
<tr>
<td>Aspirin monotherapy</td>
<td>1.73 (0.93; 2.54)</td>
<td>0.79 (0.47; 1.11)</td>
</tr>
<tr>
<td>Aspirin plus clopidogrel</td>
<td>1.46 (0.66; 2.27)</td>
<td>0.60 (0.23; 0.96)</td>
</tr>
<tr>
<td>Dose-adjusted VKA</td>
<td>-0.33 (-1.03; 0.37)</td>
<td>0.31 (-0.65; 0.03)</td>
</tr>
</tbody>
</table>

*Population rates based on trial data from all non-placebo treatment arm in included trials, ischaemic stroke rate: 2.89% and intracranial haemorrhage rate: 0.85%. *Population rates based on Danish nationwide cohort study (22), ischaemic stroke rate: 1.42% and intracranial haemorrhage rate: 0.27%. OD = once daily; VKA = vitamin K antagonist.
real-world data on the endpoint of ICH for the net clinical benefit analysis, but we recognise that some ICHs or ischaemic strokes are likely not to be diagnosed in the real world and directly result in death, which is not taken into account in the NCB definition used.

In conclusion, we show that edoxaban is likely to provide better protection from stroke and ICH than placebo, aspirin alone or aspirin plus clopidogrel in both clinical trial populations and unselected community populations. Both edoxaban doses would also bring a positive NCB compared to anti-platelet drugs or placebo/non-treatment based on ‘real world’ data.

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Conflicts of interest

A.D. Blann has received hospitality, lecture and consultancy fees from Bayer, Boehringer Ingelheim and Pfizer. F. Skjøth has nothing to declare. T. Bjerregaard Larsen has served as an investigator for Janssen Scientific Affairs, LLC and Boehringer Ingelheim. T. Bjerregaard Larsen and L. Hvilsted Rasmussen have been on the speaker bureaus for Bayer, BMS/Pfizer, Janssen Pharmaceuticals, Takeda, Roche Diagnostics and Boehringer Ingelheim. G. Y. H. Lip has received funding for research, educational symposia, consultancy, and lecturing from different manufacturers of drugs used for stroke prevention in atrial fibrillation and the treatment of thrombosis, including Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Daiichi-Sankyo, Merck, and Sanofi-Aventis.

References


Blann, Skjøth, et al. Edoxaban for stroke prevention