Net clinical benefit of new oral anticoagulants (dabigatran, rivaroxaban, apixaban) versus no treatment in a ‘real world’ atrial fibrillation population: A modelling analysis based on a nationwide cohort study

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Summary
The concept of net clinical benefit has been used to quantify the balance between risk of ischaemic stroke (IS) and risk of intracranial haemorrhage (ICH) with oral anticoagulant therapy (OAC) in the setting of non-valvular atrial fibrillation (AF), and has shown that patients at highest risk of stroke and thromboembolism gain the greatest benefit from OAC with warfarin. There are no data for the new OACs, that is, dabigatran, rivaroxaban and apixaban, as yet. We calculated the net clinical benefit balancing IS against ICH using data from the Danish National Patient Registry on patients with non-valvular AF between 1997–2008, for dabigatran, rivaroxaban and apixaban on the basis of recent clinical trial outcome data for these new OACs. In patients with CHADS2=0 but at high bleeding risk, apixaban and dabigatran 110 mg bid had a positive net clinical benefit. At CHA2DS2-VASc=1, apixaban and both doses of dabigatran (110 mg and 150 mg bid) had a positive net clinical benefit. In patients with CHADS2 score≥1 or CHA2DS2-VASc≥2, the three new OACs (dabigatran, rivaroxaban and apixaban) appear superior to warfarin for net clinical benefit, regardless of risk of bleeding. When risk of bleeding and stroke are both high, all three new drugs appear to have a greater net clinical benefit than warfarin. In the absence of head-to-head trials for these new OACs, our analysis may help inform decision making processes when all these new OACs become available to clinicians for stroke prevention in AF.

Keywords
Dabigatran, rivaroxaban, apixaban, atrial fibrillation, stroke prevention

Introduction
The concept of net clinical benefit has been used to quantify the balance between risk of ischaemic stroke (IS) and risk of intracranial haemorrhage (ICH) with oral anticoagulant therapy (OAC) in the setting of non-valvular atrial fibrillation (AF), and has shown that patients at highest risk of stroke and thromboembolism gain the greatest benefit from OAC (1). Warfarin has traditionally been the only available OAC, but several new OACs (dabigatran, rivaroxaban and apixaban) have been the subject of recent published, randomised controlled clinical trials, showing favourable effects on both IS/thromboembolism and bleeding risk (2–5). Currently, dabigatran is the only agent licensed in Europe and North America, and rivaroxaban was recently approved in the USA. Apixaban may become available in the near future, subject to regulatory approval.

The net clinical benefit of warfarin has been studied in a ‘real world’ population, but there are no data for the new OACs as yet (6). Using our previously published data for net clinical benefit calculated from the Danish National Patient Registry on patients with non-valvular AF between 1997–2008 (6), we modelled the expected net clinical benefit of dabigatran, rivaroxaban and apixaban on the basis of recent clinical trial outcomes.

Methods

Study population
The study population used for our model was the Danish National Patient Registry. Published data regarding all patients with non-valvular AF between 1997–2008 was used to calculate the net clinical benefit of warfarin. For the new OACs, data from recent clinical trials was used to estimate the risk of stroke and bleeding.

Summary
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valvular AF in the study period 1997–2008 from the National Patient Registry were used. Non-valvular AF was defined by a discharge diagnosis of AF or atrial flutter, absence of previous diagnoses of mitral or aortic valve disease, and absence of mitral or aortic valve surgery. Detailed history, including pharmacotherapy, and premorbid risk stratification scores for stroke/thromboembolism (TE) (that is, CHADS$_2$ [7], CHA$_2$DS$_2$-VASc [8]) and bleeding (HAS-BLED) are available for all patients. Published data also include outcomes, comprised of rates of stroke and thromboembolism.

Model assumptions

The event rates per 100 person years for IS (►Table 1) and ICH (►Table 2) were calculated using data from the Danish study population (6) for patients on no treatment and on warfarin, stratified by stroke risk as predicted by the CHADS$_2$ (7) and CHA$_2$DS$_2$-VASc scores (8).

Using data from recent trials of the new OACs, the event rates for IS and ICH were estimated for the Danish population. For this model, the “real world” relative risks of IS with the new agents compared to warfarin were assumed to be 0.91 for dabigatran 110 mg bid (3), 0.66 for dabigatran 150 mg bid (3), 0.88 for rivaroxaban (intention-to-treat analysis) (4), 0.79 (on-treatment analysis) (4) and 0.79 for apixaban (5). The “real world” relative risks of ICH with the new agent compared to warfarin were assumed to be 0.31 for dabigatran 110 mg bid (3), 0.40 for dabigatran 150 mg bid (3), 0.67 for rivaroxaban (4) and 0.42 for apixaban (5). The relative risks of IS and ICH were assumed to be constant across all categories of stroke risk and bleeding risk.

The event rates per 100 person years for IS (►Table 1) and ICH (►Table 2) were calculated using these relative risks and event rates on no treatment and on warfarin in the Danish study population (6), and stratified by stroke risk as predicted by the CHADS$_2$ (7) and CHA$_2$DS$_2$-VASc scores (8). The number of patients needed to treat (NNT) to prevent one IS per year was calculated as 1/ARR, where ARR is the absolute reduction, i.e. event rate on no treatment-event rate on treatment. NNT were also calculated for ICH.

The net clinical benefit was calculated using the formula \([\text{IS rate on no treatment- IS rate on anticoagulant}-1.5(\text{ICH rate on no treatment- ICH rate on anticoagulant})]\) as previously used by Singer et al. (1) for the different risk categories and stratified by CHADS$_2$ (7), CHA$_2$DS$_2$-VASc (8) and HAS-BLED (9) scoring systems.

Results

►Table 1 shows the event rates for IS per 100 person years. The overall rate of IS on no treatment was 1.00 (0.96,1.05) per 100 per-
Table 2: Event rates (95% confidence interval) for intracranial haemorrhage (ICH) per 100 person years in a 'real world' cohort adjusted for effect size from dabigatran, rivaroxaban and apixaban.

<table>
<thead>
<tr>
<th>CHADS2 score</th>
<th>No treatment</th>
<th>Warfarin</th>
<th>NNT Dabigatran 110 mg</th>
<th>NNT Dabigatran 150 mg</th>
<th>NNT Rivaroxaban</th>
<th>NNT Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.10 (0.09,0.11)</td>
<td>0.15 (0.14,0.17)</td>
<td>5000 (2000,0.05)</td>
<td>2000 (0.06,0.07)</td>
<td>2500 (0.10,0.11)</td>
<td>714 (0.15,0.17)</td>
</tr>
<tr>
<td>1</td>
<td>0.30 (0.28,0.32)</td>
<td>0.39 (0.37,0.42)</td>
<td>1111 (0.12,0.13)</td>
<td>556 (0.16,0.17)</td>
<td>714 (0.26,0.28)</td>
<td>2500 (0.16,0.18)</td>
</tr>
<tr>
<td>2–6</td>
<td>0.40 (0.38,0.42)</td>
<td>0.44 (0.41,0.46)</td>
<td>2500 (0.14,0.13)</td>
<td>385 (0.17,0.18)</td>
<td>435 (0.29,0.31)</td>
<td>909 (0.18,0.19)</td>
</tr>
</tbody>
</table>

Table 3 shows the net clinical benefit of warfarin and new oral anticoagulants (OACs) versus no treatment by stroke and bleeding risk as assessed by the CHADS2, CHA2DS2-VASc and HAS-BLED scores. As previously shown (6), the net clinical benefit balancing IS against ICH is only negative with warfarin at a CHADS2-VASc score=0. Warfarin had a positive net clinical benefit at CHADS2≥2 or CHA2DS2-VASc≥2. All new OACs were predicted to have a positive net clinical benefit in all categories of patient except those with CHADS2=0 (or CHA2DS2-VASc=0) and HAS-BLED≥3 (Fig. 1). In patients with CHADS2=0 but at high bleeding risk, apixaban and dabigatran 110 mg bid have a positive net clinical benefit. At CHA2DS2-VASc=1, apixaban and both doses of dabigatran (110 mg and 150 mg bid) have a positive net clinical benefit. In patients with CHADS2 score≥1 or CHA2DS2-VASc≥2, the three new OACs (dabigatran, rivaroxaban and apixaban) appear superior to warfarin for net clinical benefit, regardless of risk of bleeding. When risk of bleeding and stroke are both high, all three new drugs had a greater net clinical benefit than warfarin (Fig. 1).

Discussion

In our model for the present study, all new OACs (dabigatran, rivaroxaban and apixaban) are predicted to lead to lower rates of events than warfarin (Tables 1 and 2). When risk of stroke and bleeding are low, all the new OACs (dabigatran, rivaroxaban and apixaban) are superior to warfarin in terms of net clinical benefit (Table 3). As we previously reported (6), the net clinical benefit is only negative with warfarin at a CHA2DS2-VASc score=0, reflecting the ‘truly low risk’ status of these patients. Whilst the net clinical benefit for the new OACs at CHA2DS2-VASc=0 was generally favourable in this modelling exercise, the absolute event rates may be so low that a pragmatic common sense approach is needed on the necessity of even treating such ‘truly low risk’ patients with antithrombotic therapy.
In patients with CHADS\textsubscript{2}=0 but at high bleeding risk, we found apixaban and dabigatran 110 mg bid have a positive net clinical benefit when used correctly, and in the appropriate patients. Clearly, such data are not available as yet. Indeed, it must be emphasised that the Danish National Registry does reflect a ‘real world’ setting, this does not hold true for the three new OAC trials, and therefore, modelling the absolute risk of bleeding.

The net clinical benefit balancing ischaemic stroke against intracranial haemorrhage is only negative with warfarin at a CHADS\textsubscript{2}=0 score, reflecting the truly low risk status of these patients. In patients with CHADS\textsubscript{2}=0 but at high bleeding risk, apixaban and dabigatran 110 mg bid have a positive net clinical benefit. At CHADS\textsubscript{2}=1 or CHADS\textsubscript{2}-VASc=2, the three new oral anticoagulants (dabigatran, rivaroxaban and apixaban) appear superior to warfarin for net clinical benefit, regardless of risk of bleeding. When risk of bleeding and stroke are both high, all three new drugs appear to have a greater net clinical benefit than warfarin.

When compared to dose-adjusted warfarin and other OACs, demonstrated a greater net clinical benefit compared to warfarin. OACs on the basis of trial outcomes may not be the same as if decisions were based on the small absolute increase in ICH or major bleeding events.

### Table 3: Net clinical benefit of warfarin and new oral anticoagulants, versus no treatment by stroke and bleeding risk as assessed by the CHADS\textsubscript{2}, CHA\textsubscript{2}-DS\textsubscript{2}-VASc and HAS-BLED scores.

<table>
<thead>
<tr>
<th>CHADS\textsubscript{2} score</th>
<th>HAS-BLED ≤2</th>
<th>HAS-BLED ≥3</th>
<th>Dabigatran 110 mg</th>
<th>Dabigatran 150 mg</th>
<th>Rivaroxaban (ITT)</th>
<th>Rivaroxaban (OFA)</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>-0.02</td>
<td>0.19</td>
<td>1.53</td>
<td>1.74</td>
<td>1.20</td>
<td>0.68</td>
<td>0.89</td>
</tr>
<tr>
<td>(0.70,0.99)</td>
<td>(0.16,0.95)</td>
<td>(1.35,1.76)</td>
<td>(0.05,3.47)</td>
<td>(1.05,1.40)</td>
<td>(0.25,3.11)</td>
<td>(0.57,0.83)</td>
<td>(0.73,2.54)</td>
</tr>
<tr>
<td>1</td>
<td>0.84</td>
<td>0.56</td>
<td>2.14</td>
<td>1.86</td>
<td>1.84</td>
<td>1.56</td>
<td>1.14</td>
</tr>
<tr>
<td>(1.92,2.38)</td>
<td>(1.32,2.34)</td>
<td>(1.64,2.05)</td>
<td>(1.01,2.01)</td>
<td>(1.42,1.61)</td>
<td>(0.71,1.57)</td>
<td>(1.21,1.56)</td>
<td>(1.67,1.52)</td>
</tr>
<tr>
<td>2–9</td>
<td>1.95</td>
<td>3.03</td>
<td>2.74</td>
<td>3.47</td>
<td>2.42</td>
<td>2.37</td>
<td>2.37</td>
</tr>
<tr>
<td>(1.70,2.20)</td>
<td>(2.23,3.04)</td>
<td>(2.45,3.04)</td>
<td>(3.03,3.88)</td>
<td>(2.15,2.70)</td>
<td>(2.10,2.65)</td>
<td>(2.73,3.49)</td>
<td>(2.19,2.75)</td>
</tr>
<tr>
<td>CHA\textsubscript{2}-VASc score</td>
<td>0</td>
<td>0.74</td>
<td>1.36</td>
<td>1.36</td>
<td>0.62</td>
<td>0.58</td>
<td>0.84</td>
</tr>
<tr>
<td>(-0.20,-0.03)</td>
<td>(0.53,0.96)</td>
<td>(0.84,1.33)</td>
<td>(0.12,2.58)</td>
<td>(0.29,2.07)</td>
<td>(0.38,0.77)</td>
<td>(0.49,0.90)</td>
<td>(0.62,1.08)</td>
</tr>
<tr>
<td>1</td>
<td>-0.02</td>
<td>0.25</td>
<td>1.40</td>
<td>1.67</td>
<td>1.09</td>
<td>0.62</td>
<td>0.84</td>
</tr>
<tr>
<td>(-0.86,1.36)</td>
<td>(0.40,2.93)</td>
<td>(0.84,1.33)</td>
<td>(0.12,2.58)</td>
<td>(0.29,2.07)</td>
<td>(0.38,0.77)</td>
<td>(0.49,0.90)</td>
<td>(0.62,1.08)</td>
</tr>
<tr>
<td>2–9</td>
<td>1.19</td>
<td>2.21</td>
<td>2.37</td>
<td>3.39</td>
<td>2.08</td>
<td>2.15</td>
<td>2.37</td>
</tr>
<tr>
<td>(1.07,1.32)</td>
<td>(1.93,2.50)</td>
<td>(2.02,2.54)</td>
<td>(3.06,3.72)</td>
<td>(2.15,2.70)</td>
<td>(1.57,1.86)</td>
<td>(2.78,3.42)</td>
<td>(2.39,2.99)</td>
</tr>
</tbody>
</table>

What does this paper add? Several new oral anticoagulants (dabigatran, rivaroxaban and apixaban) have been the subject of recent published, randomised controlled clinical trials, showing favourable effects on both ischaemic stroke and bleeding risk. The net clinical benefit, balancing ischaemic stroke against intracranial haemorrhage, is only negative with warfarin at a CHADS\textsubscript{2}-VASc score of 0, reflecting the truly low risk status of these patients. In patients with CHADS\textsubscript{2}=0 but at high bleeding risk, apixaban and dabigatran 110 mg bid have a positive net clinical benefit. At CHADS\textsubscript{2}=1 or CHADS\textsubscript{2}-VASc=2, the three new OACs (dabigatran, rivaroxaban and apixaban) appear superior to warfarin for net clinical benefit, regardless of risk of bleeding.
We have also made no assumptions on quality of anticoagulation control with warfarin (as measured by the time in therapeutic range), which may be fairly variable in ‘real world’ cohorts and related to prognosis (11, 12). Residual confounding may also be possible given the current ‘holistic’ approach to stroke risk reduction in AF populations (13).

Conclusion
Using ‘real world’ data from the Danish National Patient Registry, we have modelled net clinical benefit data balancing IS against ICH in patients with non-valvular AF, for dabigatran, rivaroxaban and apixaban on the basis of recent clinical trial outcome data for these new OACs. When the risk of bleeding and stroke are both high, all
three new drugs appear to have a greater net clinical benefit compared to warfarin. In the absence of head-to-head trials for these new OACs, our analysis may help inform decision-making processes when all these new OACs become available for clinicians to prescribe for stroke prevention in AF.

Acknowledgements

GL provided the idea for the article and contributed to drafting and subsequent revisions. AB and DAL performed the analyses and contributed to manuscript revisions. CTP contributed to manuscript drafts and revisions. The authors take full responsibility for the content of the article. We thank Dr Jonas Olesen for his collaboration on analyses with the Danish National Patient Registry.

Conflict of interest

Prof. G.Y.H. Lip has served as a consultant for Bayer, Astellas, Merck, AstraZeneca, Sanofi, BMS/Pfizer and Boehringer, and has been on the speaker bureau for Bayer, BMS/Pfizer, Boehringer and Sanofi. Dr. D.A. Lane has received funding for research from Bayer, and been on the speaker bureau for Bayer, BMS/Pfizer and Boehringer Ingelheim. Prof. C. Torp-Pedersen has had consultancies and speaking engagements with Sanofi, Cardiome, Astellas and Merck. Dr. A. Banerjee has no conflicts of interest to report.

References