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 the use 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 $CHADS_2$=0 but at high bleeding risk, apixaban and dabigatran 110 mg bid had a positive net clinical benefit. At CHA_2DS_2-VASc=1, apixaban and both doses of dabigatran (110 mg and 150 mg bid) had a positive net clinical benefit. In patients with $CHADS_2$ score≥1 or CHA_2DS_2-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. Using 'real world' data, our modelling analysis has shown that 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.

Keywords

Dabigatran, rivaroxaban, apixaban, atrial fibrillation, stroke prevention

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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-

Table 1: Event rates (95% confidence interval) for ischaemic stroke (IS) per 100 person years in a 'real world' cohort adjusted for effect size from dabigatran, rivaroxaban and apixaban.

	No treatment	Warfarin	NNT	Dabigatran 110 mg	NNT	Dabigatran 150 mg	NNT	Rivaroxaban (ITT)	NNT	Rivaroxaban (OTA)	NNT	Apixaban	NNT
$CHADS_2$ score													
0	0.20 (0.18,0.22)	0.10 (0.09,0.11)	1000	0.09 (0.08,0.10)	880	0.06 (0.06,0.07)	732	0.08 (0.08,0.1)	812	0.08 (0.07,0.09)	805	0.08 (0.07,0.90)	805
1	1.00 (0.92,1.09)	0.50 (0.46,0.55)	200	0.46 (0.42,0.50)	182	0.33 (0.3,0.36)	149	0.44 (0.40,0.48)	167	0.40 (0.36,0.43)	165	0.40 (0.36,0.43)	165
2–6	3.01 (2.85,3.16)	1.65 (1.56,1.74)	74	1.50 (1.42,1.58)	66	1.09 (1.03,1.15)	52	1.45 (1.37,1.53)	60	1.30 (1.23,1.37)	59	1.30 (1.23,1.37)	59
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)	2989	0.03 (0.02,0.03)	2315	0.04 (0.03,0.04)	2665	0.03 (0.03,0.04)	2637	0.03 (0.03,0.04)	2637
1	0.10 (0.09,0.12)	0.05 (0.04,0.06)	2000	0.04 (0.04,0.05)	1761	0.03 (0.03,0.04)	1464	0.04 (0.04,0.05)	1623	0.04 (0.03,0.04)	1611	0.04 (0.03,0.04)	1611
2–9	2.00 (1.91,2.10)	1.08 (1.02,1.12)	109	0.98 (0.93,1.02)	97	0.71 (0.67,0.74)	78	0.95 (0.90,0.99)	88	0.85 (0.81,0.88)	87	0.85 (0.81,0.88)	87
Overall	1.00 (0.96,1.05)	0.53 (0.51,0.56)	213	0.48 (0.46,0.51)	191	0.35 (0.34,0.37)	154	0.47 (0.45,0.49)	174	0.42 (0.40,0.44)	172	0.42 (0.40,0.44)	172

ITT: Intention-to-treat analysis; OTA: On treatment analysis. NNT: number of patients needed to treat to prevent one ischaemic stroke per year. NNT is calculated as 1/ARR, where ARR is the absolute reduction, i.e. event rate on no treatment-event rate on treatment. These data were derived from the Danish National Patient Registry, where all patients discharged with non-valvular AF in Denmark were identified (n=132,372) as described by Olesen et al. (6). Patients were followed up from index AF discharge and throughout the study period, i.e. maximum 12 years of follow-up.

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_2DS_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_2DS_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_2DS_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 was the absolute reduction, i.e. event rate on no treatment-event rate on treatment. NNT were also calculated for ICH. A *negative value for NNT* denotes the "number needed to harm", i.e. the number of patients needed to treat to cause an ICH.

The net clinical benefit was calculated using the formula [(IS rate on no treatment- IS rate on anticoagulant)-1.5(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_2DS_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.

	No treatment	Warfarin	NNT	Dabigatran 110 mg	NNT	Dabigatran 150 mg	NNT	Rivaroxaban	NNT	Apixaban	NNT
$CHADS_2$ score											
0	0.10 (0.09,0.11)	0.15 (0.14,0.17)	–2000	0.05 (0.04,0.05)	2000	0.06 (0.06,0.07)	2500	0.10 (0.10,0.11)	-	0.06 (0.06,0.07)	2500
1	0.30 (0.28,0.32)	0.39 (0.37,0.42)	–1111	0.12 (0.11,0.13)	556	0.16 (0.15,0.17)	714	0.26 (0.25,0.28)	2500	0.16 (0.15,0.18)	714
2–6	0.40 (0.38,0.42)	0.44 (0.41,0.46)	–2500	0.14 (0.13,0.14)	385	0.17 (0.16,0.18)	435	0.29 (0.28,0.31)	909	0.18 (0.17,0.19)	455
CHA_2DS_2-VASc score											
0	0.05 (0.04,0.06)	0.09 (0.08,0.11)	–2500	0.03 (0.02,0.03)	5000	0.04 (0.03,0.04)	10000	0.06 (0.05,0.07)	–10000	0.04 (0.03,0.05)	10000
1	0.10 (0.09,0.11)	0.14 (0.13,0.16)	–2500	0.04 (0.04,0.05)	1667	0.06 (0.05,0.06)	2500	0.09 (0.08,0.10)	10000	0.06 (0.05,0.07)	2500
2–9	0.30 (0.29,0.31)	0.36 (0.34,0.37)	–1667	0.11 (0.11,0.11)	526	0.14 (0.14,0.15)	625	0.24 (0.23,0.25)	1667	0.15 (0.14,0.15)	667
Overall	0.30 (0.29,0.31)	0.44 (0.42,0.45)	–714	0.14 (0.13,0.14)	625	0.18 (0.17,0.18)	833	0.29 (0.28,0.30)	10000	0.18 (0.18,0.19)	833

ITT: Intention-to-treat analysis; OTA: On treatment analysis. NNT: number of patients needed to treat to prevent one intracranial haemorrhage per year. A negative value for NNT denotes the "number needed to harm", i.e. the number of patients needed to treat to cause an intracranial haemorrhage. NNT is calculated as 1/ARR, where ARR is the absolute reduction, i.e. event rate on no treatment-event rate on treatment. These data were derived from the Danish National Patient Registry, where all patients discharged with non-valvular AF in Denmark were identified (n=132,372) as described by Olesen et al. (6). Patients were followed up from index AF discharge and throughout the study period, i.e. maximum 12 years of follow-up.

son years. On warfarin, the overall rate was 0.53 (0.51,0.56) per 100 person years and the NNT to prevent 1 IS was 213 per year. In our model, all of the new OACs had lower predicted IS rates than warfarin, with dabigatran 150 mg bid having the lowest rate of 0.35 (0.34,0.37) per 100 person years with a NNT of 154. For all new OACs, the IS event rate increased with increasing $CHADS_2$ and CHA_2DS_2-VASc scores.

The NNTs at $CHADS_2 \geq 2$ were 74 for warfarin, 66 for dabigatran 110 mg bid, 52 for dabigatran 150 mg bid, 60 for rivaroxaban (intention-to-treat analysis) and 59 for apixaban, respectively. The corresponding NNTs at CHA_2DS_2-VASc ≥2 were 109 for warfarin, 97 for dabigatran 110 mg bid, 78 for dabigatran 150 mg bid, 88 for rivaroxaban (intention-to-treat analysis) and 87 for apixaban, respectively.

►Table 2 shows the event rates for haemorrhagic stroke per 100 person years. The overall rate of ICH on no treatment was 0.30(0.29,0.31) per 100 person years. On warfarin, the overall rate was 0.44(0.42,0.45) per 100 person years and the NNH to cause 1 ICH was 714 per year. In our model, all of the new OACs had lower predicted ICH rates than warfarin, in that the NNTs were all positive. Dabigatran 110 mg bid had the lowest rate of ICH of 0.14 (0.13,0.14) per 100 person years and the NNT was 625 to prevent 1 ICH. As with IS, for all agents, the event rate increased with increasing $CHADS_2$ and CHA_2DS_2-VASc scores.

The NNTs at $CHADS_2 \geq 2$ were –2500 for warfarin, 385 for dabigatran 110 mg, 435 for 150 mg, 909 for rivaroxaban and 455 for apixaban, respectively. The corresponding NNTs at CHA_2DS_2-VASc ≥2 were –1667 for warfarin, 526 for dabigatran 110 mg bid, 625 for dabigatran 150 mg bid, 667 for rivaroxaban (intention-to-treat analysis) and 87 for apixaban, respectively.

►Table 3 shows the net clinical benefit of warfarin and new OACs versus no treatment by stroke and bleeding risk as assessed by the $CHADS_2$, CHA_2DS_2-VASc and HAS-BLED scores. As previously shown (6), the net clinical benefit balancing IS against ICH is only negative with warfarin at a CHA_2DS_2-VASc score=0. Warfarin had a positive net clinical benefit at $CHADS_2 \geq 1$ or CHA_2DS_2-VASc≥2. All new OACs were predicted to have a positive net clinical benefit in all categories of patient except those with $CHADS_2$=0 (or CHA_2DS_2-VASc=0) and HAS-BLED≥3 (►Fig. 1).

In patients with $CHADS_2$=0 but at high bleeding risk, apixaban and dabigatran 110 mg bid have a positive net clinical benefit. At CHA_2DS_2-VASc=1, apixaban and both doses of dabigatran (110 mg and 150 mg bid) have a positive net clinical benefit. In patients with $CHADS_2$ score≥1 or CHA_2DS_2-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 CHA_2DS_2-VASc score=0, reflecting the 'truly low risk' status of these patients. Whilst the net clinical benefit for the new OACs at CHA_2DS_2-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.

Table 3: Net clinical benefit of warfarin and new oral anticoagulants, versus no treatment by stroke and bleeding risk as assessed by the $CHADS_2$, CHA_2DS_2-VASc and HAS-BLED scores.

	Net clinical benefit (95% confidence interval) of oral anticoagulant versus no treatment											
	Warfarin		Dabigatran 110 mg		Dabigatran 150 mg		Rivaroxaban (ITT)		Rivaroxaban (OTA)		Apixaban	
	HAS-BLED ≤2	HAS-BLED ≥3	HAS-BLED ≤2	HAS-BLED ≥3	HAS-BLED ≤2	HAS-BLED ≥3	HAS-BLED ≤2	HAS-BLED ≥3	HAS-BLED ≤2	HAS-BLED ≥3	HAS-BLED ≤2	HAS-BLED ≥3
$CHADS_2$ score												
0	−0.02 (-0.09,0.06)	0.19 (-1.39,1.77)	1.53 (1.35,1.76)	1.74 (0.05,3.47)	1.20 (1.05,1.40)	1.41 (-0.25,3.11)	0.68 (0.57,0.83)	0.89 (-0.73,2.54)	0.64 (0.53,0.78)	0.85 (-0.77,2.49)	0.77 (0.65,0.93)	1.22 (1.06 , 1.42)
1	0.84 (0.70,0.99)	0.56 (0.16,0.95)	2.14 (1.92,2.38)	1.86 (1.38,2.34)	1.84 (1.64,2.05)	1.56 (1.10,2.01)	1.42 (1.25,1.61)	1.14 (0.71,1.57)	1.38 (1.21,1.56)	1.10 (0.67,1.52)	1.49 (1.31,1.68)	1.87 (1.66 , 2.08)
2–6	1.95 (1.70,2.20)	2.68 (2.33,3.04)	3.03 (2.72,3.34)	3.76 (3.35,4.18)	2.74 (2.45,3.04)	3.47 (3.08,3.88)	2.42 (2.15,2.70)	3.15 (2.78,3.54)	2.37 (2.10,2.65)	3.10 (2.73,3.49)	2.47 (2.19,2.75)	2.78 (2.49,3.08)
CHA_2DS_2-VASc score												
0	−0.11 (-0.20,-0.03)	-	1.75 (1.40,2.15)	-	1.36 (1.07,1.68)	-	0.74 (0.53,0.96)	-	0.68 (0.49,0.89)	-	0.84 (0.62,1.08)	-
1	−0.02 (-0.15,0.11)	0.25 (-0.86,1.36)	1.40 (1.11,1.68)	1.67 (0.40,2.93)	1.09 (0.84,1.33)	1.36 (0.13,2.58)	0.62 (0.42,0.82)	0.89 (-0.29,2.07)	0.58 (0.38,0.77)	0.85 (-0.33,2.02)	0.70 (0.49,0.90)	1.11 (0.85,1.35)
2–9	1.19 (1.07,1.32)	2.21 (1.93,2.50)	2.37 (2.20,2.54)	3.39 (3.06,3.72)	2.08 (1.92,2.24)	3.10 (2.78,3.42)	1.71 (1.57,1.86)	2.73 (2.43,3.04)	1.67 (1.53,1.81)	2.69 (2.39,2.99)	1.77 (1.62,1.92)	2.11 (1.95,2.27)

Net clinical benefit [Events Prevented per 100 Person-Years (95% Confidence Interval)] is calculated as annualised (thromboembolism rate $_{\text{off warfarin}}$ – thromboembolism rate $_{\text{on warfarin}}$) – 1.5*x* (ICH rate $_{\text{on warfarin}}$ – ICH rate $_{\text{off warfarin}}$), based on the study by Singer et al[1]. ITT: Intention-to-treat analysis; OTA: On treatment analysis.

In patients with $CHADS_2$=0 but at high bleeding risk, we found apixaban and dabigatran 110 mg bid have a positive net clinical benefit, when compared to others. At CHA_2DS_2-VASc=1, only apixaban and both doses of dabigatran (110 mg and 150 mg bid) appeared have a positive net clinical benefit. In patients with $CHADS_2$ score≥1 or CHA_2DS_2-VASc≥2, the three new drugs did better than warfarin for net clinical benefit, regardless of risk of bleeding.

When risk of bleeding and stroke are both high, all three new OACs demonstrated a greater net clinical benefit compared to warfarin. For net clinical benefit. Patients with a high HAS-BLED score ≥3 generally had a greater net clinical benefit with any OAC (whether warfarin or a new agent), given that higher bleeding risk individuals would also be at high IS risk, and have a much greater absolute reduction in stroke risk with OAC, which would outweigh the small absolute increase in ICH (or major bleeding) events (10).

Limitations

Whereas 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 expected net clinical benefit of the new OACs on the basis of trial outcomes may not be the same as if derived from a 'real world' clinical registry of these new drugs (and such data are not available as yet). Indeed, it must be emphasised that all the new OACs are powerful anticoagulants, and would work well if used correctly, and in the appropriate patients. Clearly, when used inappropriately (e.g. in AF patients with renal failure), the risk of major adverse events is high.

What is known about this topic?

- 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/thromboembolism and bleeding risk.
- The net clinical benefit balancing ischaemic stroke against intracranial haemorrhage is only negative with warfarin at a CHA_2DS_2-VASc score=0, reflecting the 'truly low risk' status of these patients.

What does this paper add?

- In patients with $CHADS_2$=0 but at high bleeding risk, apixaban and dabigatran 110 mg bid have a positive net clinical benefit.
- At CHA_2DS_2-VASc=1, apixaban and both doses of dabigatran (110 mg and 150 mg bid) have a positive net clinical benefit.
- In patients with $CHADS_2$ score≥1 or CHA_2DS_2-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.

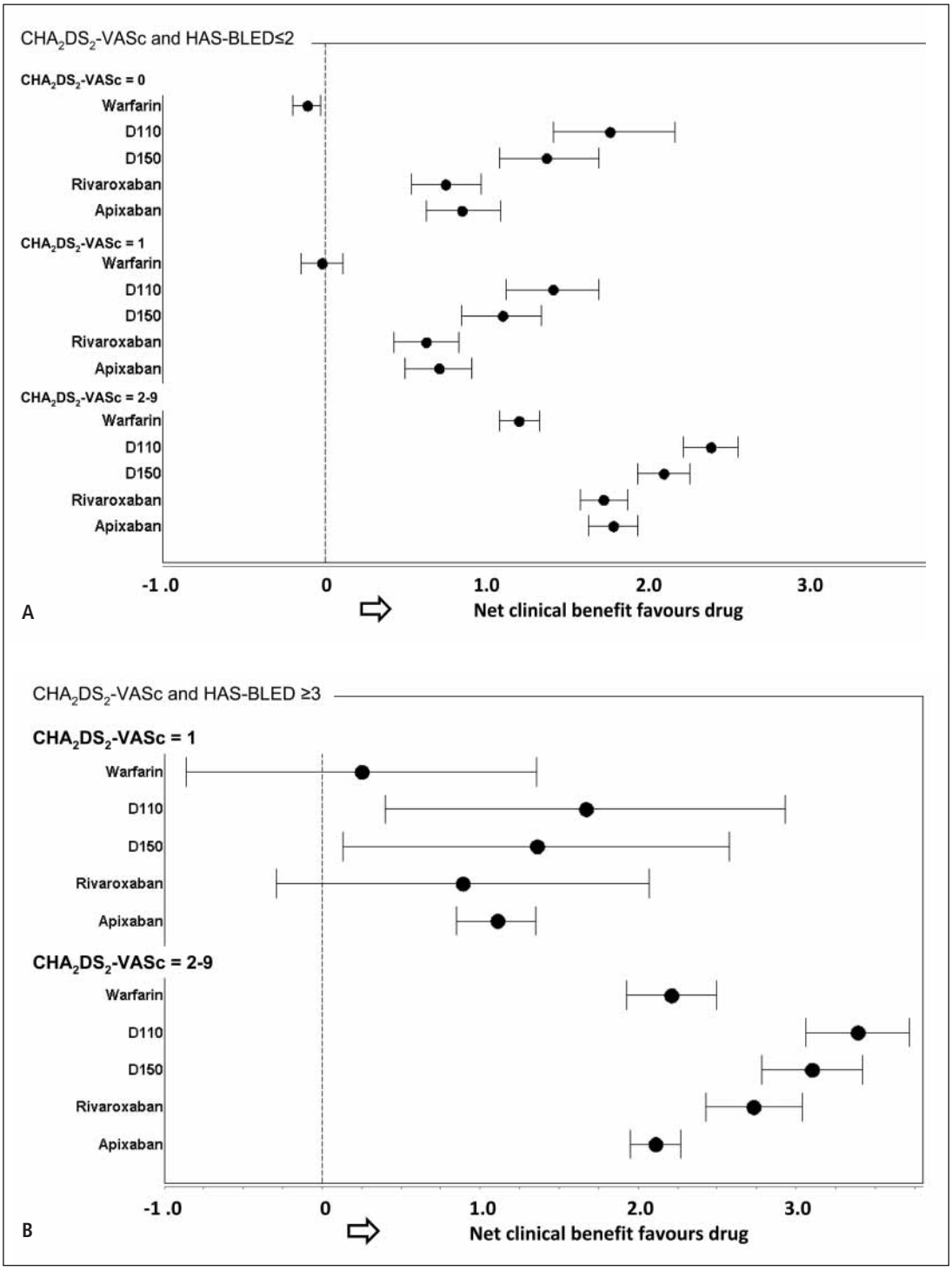

Figure 1: Net clinical benefit for warfarin, dabigatran, rivaroxaban and apixaban by CHA_2DS_2-VASc and HAS-BLED scores. A) HAS-BLED ≤2. B) HAS-BLED ≥3. For HAS-BLED ≥3, there were no data with CHA_2DS_2-VASc score=0. Rivaroxaban (intention-to-treat) data shown. D110: dabigatran 110 mg; D150: dabigatran 150 mg.

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.

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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

1. Singer DE, Chang Y, Fang MC, et al. The net clinical benefit of warfarin anticoagulation in atrial fibrillation. Ann Intern Med 2009; 151: 297–305.
2. Ahrens I, Lip GY, Peter K. New oral anticoagulant drugs in cardiovascular disease. Thromb Haemost 2010; 104: 49–60.
3. Connolly SJ, Ezekowitz MD, Yusuf S, et al.; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009; 361: 1139–1151.
4. Patel MR, Mahaffey KW, Garg J, et al.; ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011; 365: 883–891.
5. Granger CB, Alexander JH, McMurray JJ, et al.; ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011; 365: 981–992.
6. Olesen JB, Lip GY, Lindhardsen J, et al. Risks of thromboembolism and bleeding with thromboprophylaxis in patients with atrial fibrillation: A net clinical benefit analysis using a 'real world' nationwide cohort study. Thromb Haemost 2011; 106: 739–749.
7. Gage BF, Waterman AD, Shannon W, et al. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation". J Am Med Assoc 2001; 285: 2864–2870.
8. Lip GY, Nieuwlaat R, Pisters R, et al. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on atrial fibrillation. Chest 2010; 137: 263–272.
9. Pisters R, Lane DA, Nieuwlaat R, et al. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest. 2010; 138: 1093–1100.
10. Lip GY, Andreotti F, Fauchier L, et al. Bleeding risk assessment and management in atrial fibrillation patients. Executive Summary of a Position Document from the European Heart Rhythm Association [EHRA], endorsed by the European Society of Cardiology [ESC] Working Group on Thrombosis. Thromb Haemost 2011; 106: 997–1011.
11. Apostolakis S, Lip GY. Stroke prevention in non-valvular atrial fibrillation: Can warfarin do better? Thromb Haemost 2011; 106: 753–754.
12. Gallagher AM, Setakis E, Plumb JM, et al. Risks of stroke and mortality associated with suboptimal anticoagulation in atrial fibrillation patients. Thromb Haemost 2011; 106: 968–977.
13. Kirchhof P, Lip GY, Van Gelder IC, et al. Comprehensive risk reduction in patients with atrial fibrillation: Emerging diagnostic and therapeutic options. Executive summary of the report from the 3rd AFNET/EHRA consensus conference. Thromb Haemost 2011; 106: 1012–1019.

