Utilizzo degli ABC-AF risk score per valutare il beneficio clinico netto della terapia anticoagulante orale nel paziente con fibrillazione atriale

Background

- Decisions on stroke prevention strategies in patients with atrial fibrillation (AF) ideally rely on estimating and balancing the risks of stroke and bleeding with different treatment alternatives.
- However, the current guideline recommended risk scores in AF do not allow precise quantification of risks with different treatments in order to optimize the balancing of stroke and major bleeding risks.
- Additionally, the formal recommendation regarding oral anticoagulation (OAC) vs no-OAC is currently based on the patient's estimated stroke risk, not accounting for bleeding risk, which may introduce a risk of net harm.

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Background

- The biomarker-based ABC-AF risk scores for stroke and bleeding are currently the only available tools validated and calibrated for different antithrombotic treatments that provide quantitative estimates of continuous risks with different treatment strategies.
- The aim of this study was to identify clinically relevant thresholds for OAC treatment in the individual patient with AF.
- The study compared the observed 1-year risk in patients with OAC in the ARISTOTLE and RE-LY trials with the predicted 1-year risk if the same patients would not have received OAC using the biomarker-based ABC-AF stroke and bleeding risk scores.

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ABC-risk scores

• **ABC-AF risk score for stroke**	• **ABC-AF risk score for bleeding**

• **Age**
• **Biomarkers**
  • N-terminal pro-B-type natriuretic peptide [NT-proBNP]
  • Cardiac troponin T [cTnT-hs]
• **Clinical history** of prior stroke/TIA
	• **Age**
	• **Biomarkers**
	  • hemoglobin
	  • growth differentiation factor 15 [GDF-15]
	  • cTnT-hs
	• **Clinical history** of prior bleeding

The ABC-AF risk scores were developed and validated in patients with AF treated with OAC, and also validated in and recalibrated for patients with AF treated with aspirin, but not OAC, using data from the ACTIVE and AVERROES cohorts.

Eur Heart J, 37 (2016), pp. 1582-1590
Lancet, 387 (2016), pp. 2302-2311

Individual net clinical outcome with oral anticoagulation in atrial fibrillation using the ABC-AF risk scores

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Methods

- Patients with AF receiving OAC treatment in the randomized ARISTOTLE and RE-LY trials, with available biomarkers for calculation of ABC-AF scores at baseline, were included (n = 23,121).
- Observed 1-year risk on OAC was compared with predicted 1-year risk if the same patients would not have received OAC using the ABC-AF scores calibrated for aspirin. Net clinical outcome was defined as the sum of stroke and major bleeding risks.

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Baseline characteristics

Variable	Combined OAC cohort (n = 23,121)
Randomized treatment: apixaban	31.9% (7,372)
Randomized treatment: dabigatran 110 mg	12.1% (2,805)
Randomized treatment: dabigatran 150 mg	12.1% (2,801)
Randomized treatment: warfarin	43.9% (10,143)
Age (years)	71.0 (64.0-76.0)
Sex (female)	35.9% (8,299)
Body mass index (kg/m^2)	28.3 (25.2-32.1) [74]
Current smoker	8.0% (1,840) [14]
Diabetes	23.8% (5,509)
Heart failure	30.2% (6,973)
Hypertension	84.4% (19,506)
Myocardial infarction	14.3% (3,306) [1]
Peripheral artery disease	4.4% (1,021) [2]
Permanent or persistent AF	78.5% (18,146) [7]
Prior bleeding	15.1% (3,501)
Prior stroke/transient ischemic attack	19.0% (4,389)
Vascular disease	22.8% (5,278)
CHA_2DS_2-VASc score	3.0 (2.0-4.0)
HAS-BLED score	2.0 (1.0-2.0)
Hemoglobin (g/dL)	14.3 (13.2-15.3)
NT-proBNP (ng/L)	744.0 (372.0-1,325.0)
GDF-15 (ng/L)	1,436.0 (1,024.0-2,107.0)
Troponin T (hs) (ng/L)	11.4 (7.6-17.6)
ABC-AF-stroke risk (%)	1.2 (0.9-1.8)
ABC-AF-bleeding risk (%)	2.1 (1.4-3.3)

m (a - b) represents median (Q_1 - Q_3). p% (n) represent percentage (frequency).
Percentages computed by group. [M] represents number of missing.
OAC - oral anticoagulation; AF - atrial fibrillation

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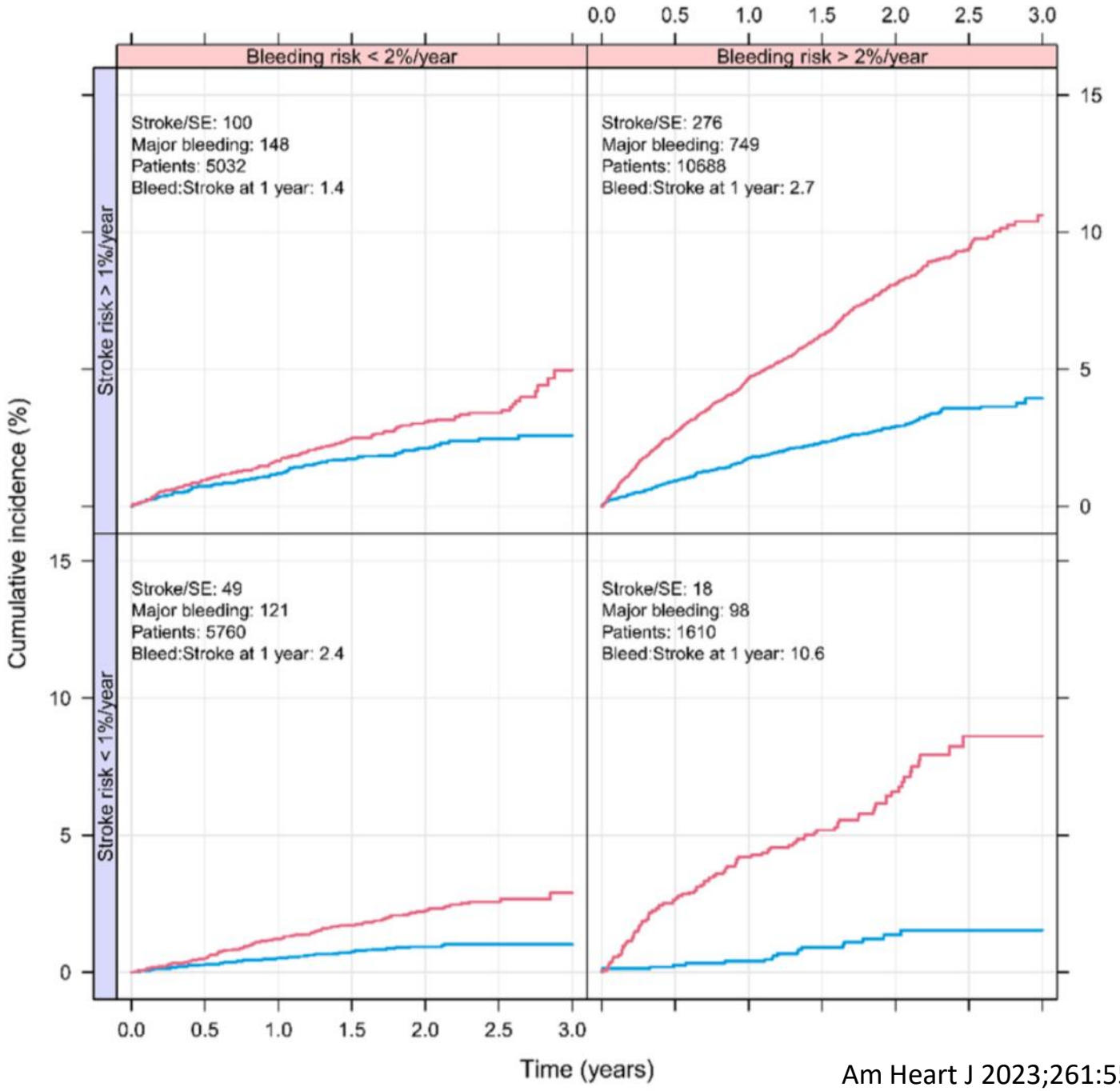
Cumulative incidence of stroke and major bleeding by different ABC-AF risk profiles

- The estimated annual risk of stroke according to the ABC-AF-stroke score is shown in the blue rows and can be "low" (<1%) or "high" (>1%).
- The estimated risk of major bleeding according to the ABC-AF-bleeding score is shown in the red columns and can be "low" (<2%) or "high" (>2%).
- Bleed:Stroke at 1 year estimated relative cumulative incidence of bleeding to incidence of stroke at 1 year.
- Note that, the cut-offs are arbitrary and used to visualize risk profiles and the relative risk ratios between major bleeding and stroke between the risk classes.



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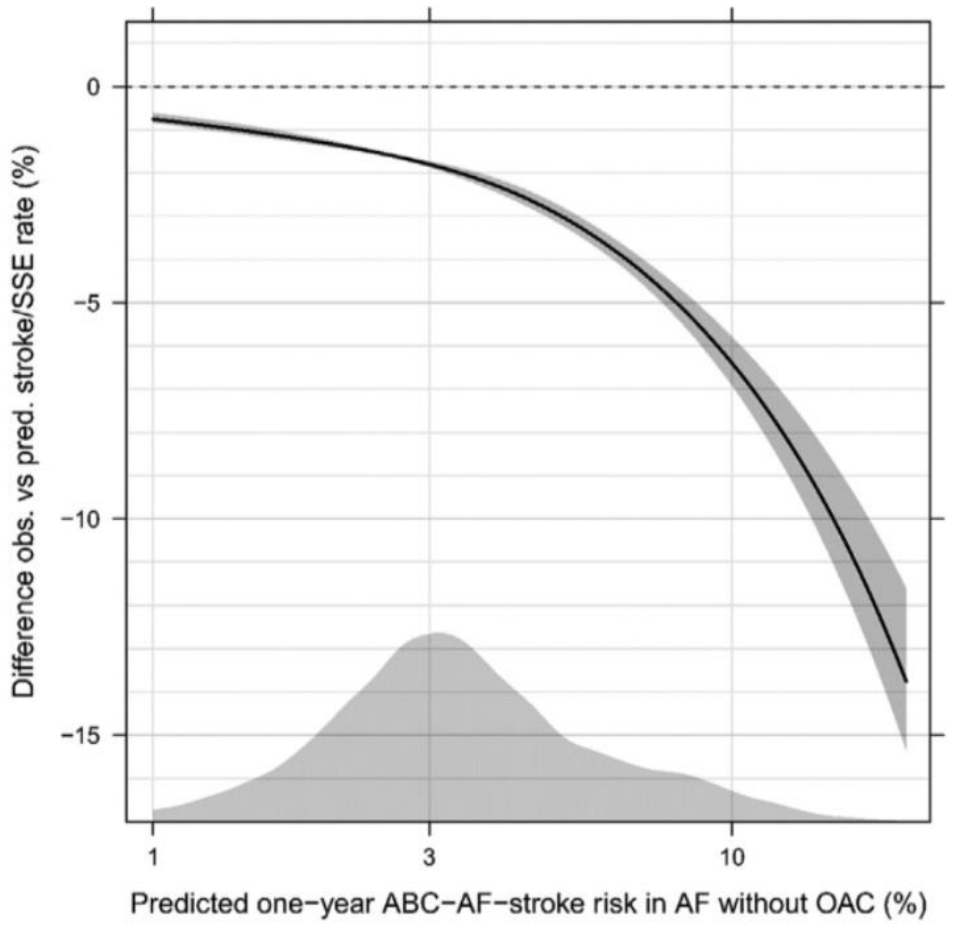
Difference between observed stroke/systemic embolism 1-year risk with OAC treatment vs no OAC in relation to the ABC-AF-stroke score.
A distribution plot of the ABC-AF-stroke risk score is shown in the bottom part of the figure



Difference between observed major bleeding 1-year risk, during OAC treatment vs no-OAC in relation to the ABC- AF-bleeding score.
A distribution plot of the ABC-AF-bleeding risk score is shown in the bottom part of the figure.

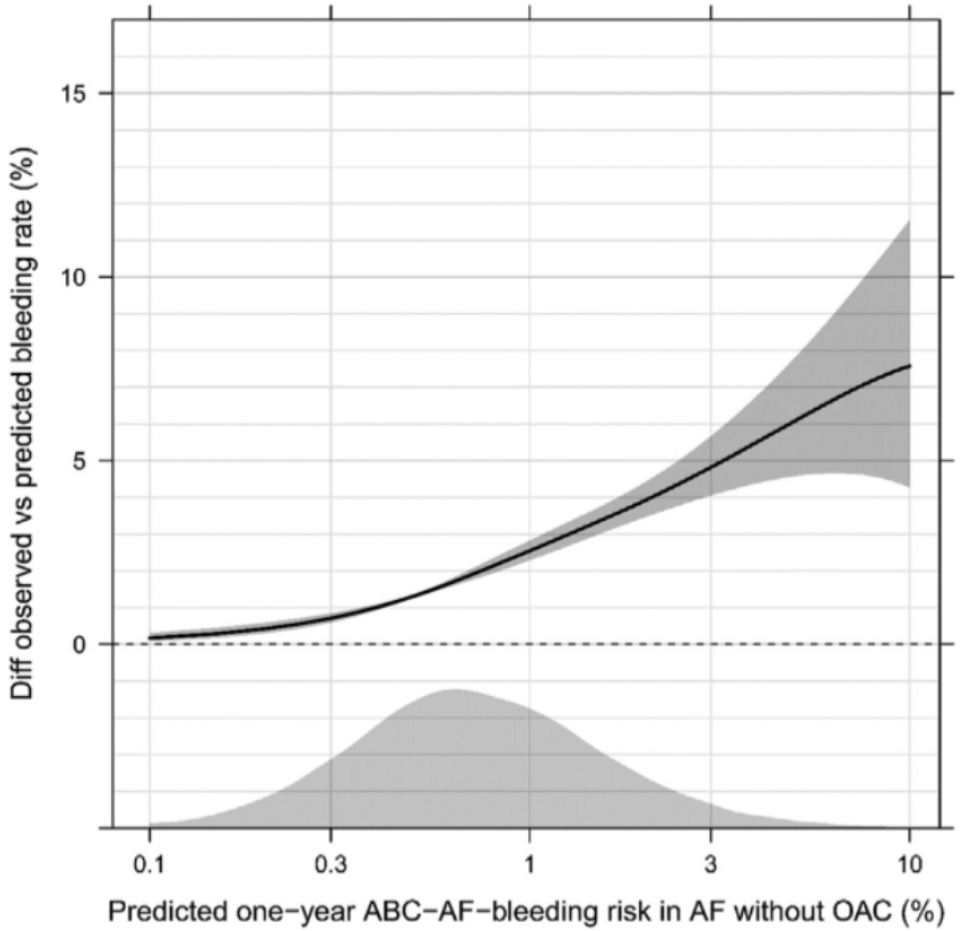


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Illustration of the unweighted net clinical outcome, defined as the sum of the estimated ABC-AF-stroke and ABC-AF-bleeding risk (1)

- Equal net clinical outcome with or without OAC is indicated by the solid bold line. Net clinical outcome with OAC is indicated by the solid diagonal lines. Net clinical outcome without OAC is indicated by the dashed contour lines.
- **Example 1**. The **solid dot** shows a patient with an ABC-AF-stroke risk with OAC of 1% and an ABC-AF-bleeding risk with OAC of 2%. Thus, the net clinical outcome with OAC (the sum of the risks) is 1% + 2% = 3% and the dot therefore lies halfway between the solid 0.02 and 0.04 grid lines. Using the mathematical relation, a net clinical outcome without OAC can be estimated. Roughly, for low risks, the stroke risk is 3 times larger and the bleeding risk is half without OAC as compared with OAC. Thus, the patient in example 1 has a net clinical outcome without OAC equal to 1% × 3 + 2% × 0.5 = 4% and the solid dot therefore lies on the dashed 0.04 line. This patient has a lower net clinical outcome with OAC (0.03) than without OAC (0.04), and therefore has a **net benefit with OAC treatment.**

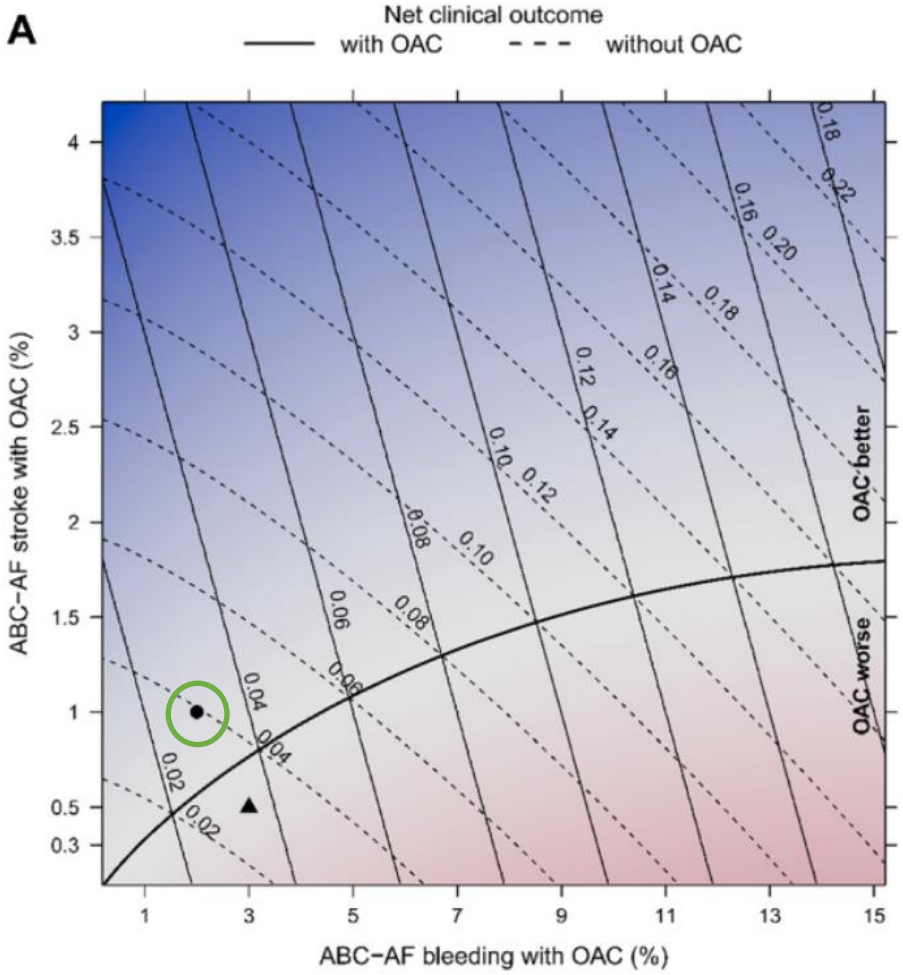

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Illustration of the unweighted net clinical outcome, defined as the sum of the estimated ABC-AF-stroke and ABC-AF-bleeding risk (2)

- **Example 2.** The **solid triangle** shows a patient with an ABC-AF-stroke risk with OAC of 0.5% and an ABC-AF-bleeding risk with OAC of 3%. The corresponding net clinical outcome with OAC is therefore 0.5% + 3% = 3.5% and the triangle therefore lies 3/4 between the solid 0.02 and 0.04 lines. Correspondingly, the patient in example 2 has a net clinical outcome without OAC equal to: 0.5% × 3 + 3% × 0.5 = 3% and the triangle therefore lies halfway between the dashed 0.02 and 0.04 lines. This patient, thus, has a higher net clinical outcome with OAC (0.035) than without OAC (0.03), and therefore has a **net harm with OAC treatment**.

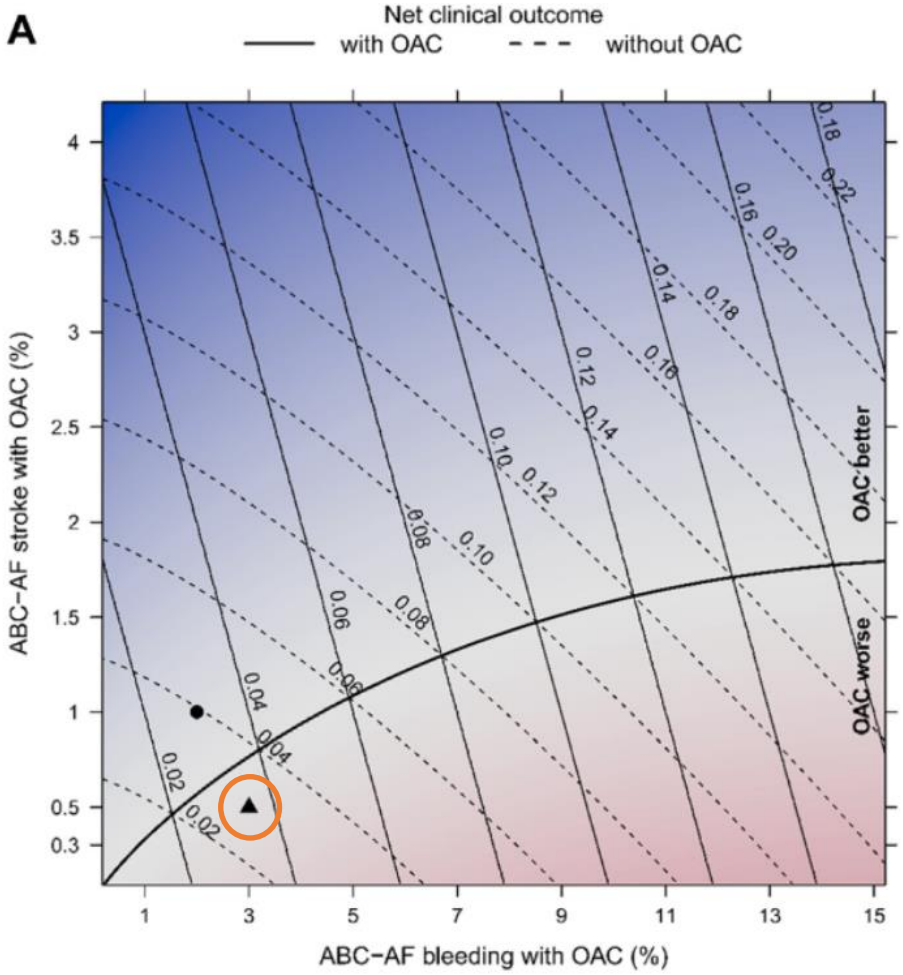

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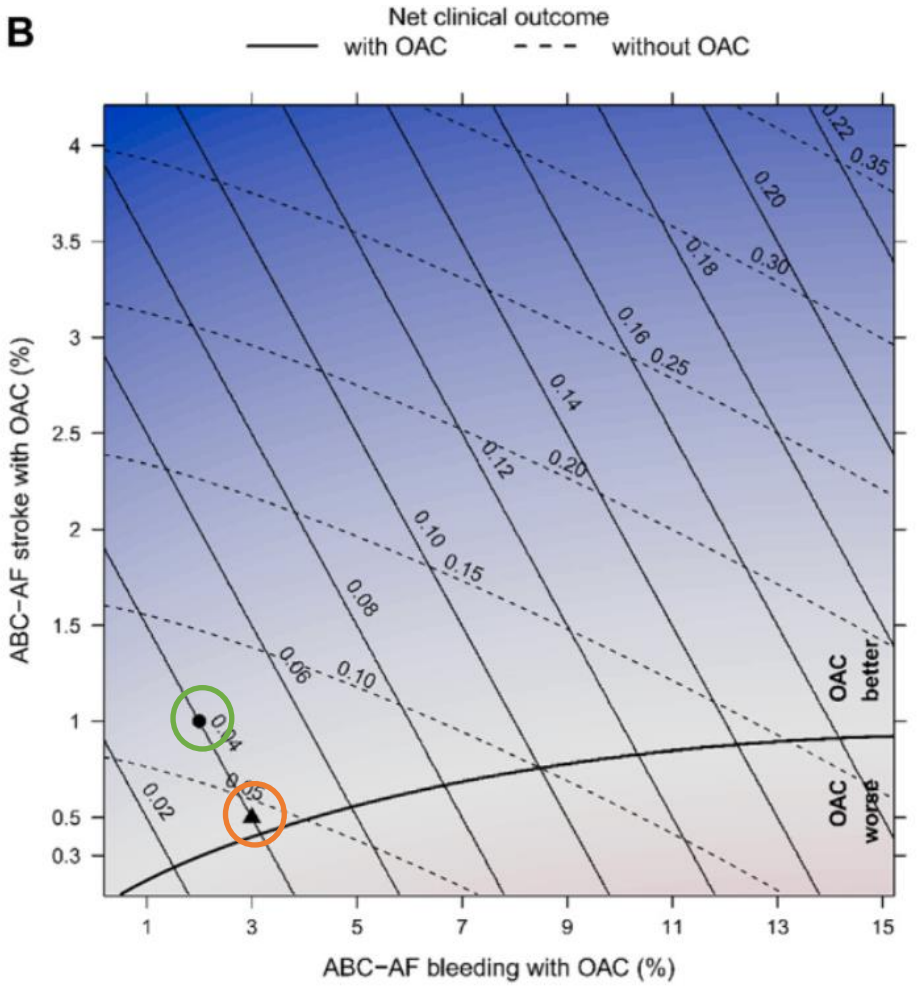
Illustration of the weighted net clinical outcome, defined as the sum of the estimated ABC-AF-stroke and ABC-AF-bleeding risk

- Net clinical outcome for different combinations of ABC-AF-stroke and ABC-AF-bleeding risks in **weighted models** assigning a stroke to be twice as harmful as a major bleeding. Thus, net clinical outcome is calculated as twice the estimated stroke risk plus the estimated bleeding risk.
- Under this assumption of weighted risks, the 2-example patients now both have higher net clinical outcome without OAC.
- The **solid circle,** lies on the 0.04 solid line because the weighted sum with OAC is given by 2 × 1% + 2% = 4% while the weighted net clinical outcome without OAC is approximately 2 × 1% × 3 + 2% × 0.5 = 7% which is 2/5 between the dashed 0.05 and 0.10 lines.
- The **solid triangle** also lies on the solid 0.04 line since the weighted net clinical outcome with OAC is: 2 × 0.5% + 3% = 4% while the net clinical outcome without OAC is approximately 2 × 0.5% × 3 + 3% × 0.5 = 4.5%, which corresponds to the position just lower than the dashed 0.05 line. Thus, based on the weighting scheme, the net benefit is now in favor of OAC treatment for the patient in example 2.



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http://www.abc-score.com/abcaf/

Limitations

- The present study was based on 2 large clinical trial cohorts that excluded patients with severe renal dysfunction or short life expectancy.
- Additionally, the net clinical outcome analysis may be limited by some overlap since hemorrhagic strokes were included in both the primary efficacy (all strokes) and the primary safety (major bleedings) outcomes according to the prespecified trial protocols.
- Due to slightly different inclusion criteria in the trials and smaller subgroup sample sizes over the continuously estimated ABC-AF risk, subanalyses comparing the different OAC compounds were not performed.
- Another issue that merits additional consideration is the weighing of stroke and bleeding risk, as they carry different clinical importance. As such, data were provided for both unweighted and weighted models, and may thus be further tuned including different weighing, and individual patient preferences.

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Conclusions

- In patients with AF, integrated use of the ABC-AF-stroke and ABC-AF-bleeding risk scores allows an individual quantitative continuous estimation of the balance between benefits and risks with different antithrombotic treatment alternatives.
- This precision medicine tool seems useful as decision support. This net clinical outcome model of the ABC-AF scores may be digitally implemented, thereby directly visualizing the net clinical benefit or harm with OAC treatment for the individual patient.

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