PREDICTORS OF GASTROINTESTINAL BLEEDING IN AF

PATIENT-LEVEL ANALYSIS OF LARGE-SCALE RANDOMIZED TRIALS FROM COMBINE AF

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BACKGROUND

Gastrointestinal (GI) bleeding is the most common type of bleeding in patients with AF on oral anticoagulation. Reliably characterizing independent predictors of GI bleeding may help identify higher risk patients.

OBJECTIVE

We aimed to assess incidence and independent predictors of GI bleeding, according to the International Society on Thrombosis and Hemostasis (ISTH) definitions of severity.

METHODS

Individual patient data from the four, large-scale, pivotal phase III randomized trials comparing direct oral anticoagulants with warfarin for stroke prevention in AF (RE-LY, ROCKET AF, ARISTOTLE and ENGAGE AF-TIMI 48) were pooled to create the COMBINE AF) dataset.

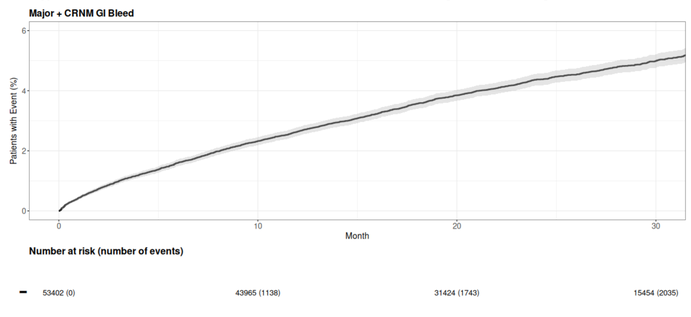
We specified covariates with established bleeding associations and employed backwards selection models to identify additional covariates associated with GI bleeding in the safety population of the COMBINE AF dataset.

A multivariable Cox proportional hazards regression model was fitted to identify independent predictors of GI bleeding, according to the following definitions:

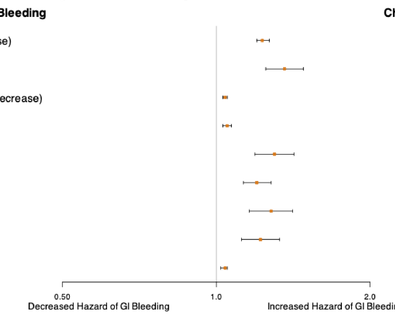
1) **The composite of ISTH major or clinically relevant non-major (CRNM) GI bleeding**
2) **ISTH major GI bleeding**

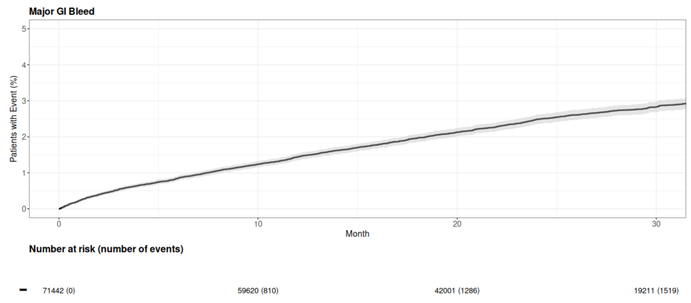
RESULTS

Figure. Cumulative incidence and independent predictors of GI bleeding, ordered by the chi-square statistic contribution to model fit

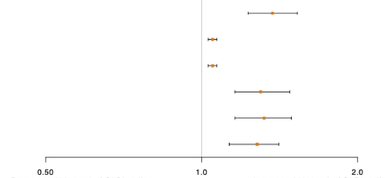


Predictors of Major or CRNM GI Bleeding	Chi-Square Statistic	HR [95%CI]	P-Value
Hemoglobin level (per 1-g/dL decrease)	209.01	1.23 [1.20,1.27]	<0.001
Antiplatelet use	49.20	1.36 [1.25,1.48]	<0.001
Creatinine clearance (per 5 mL/min decrease)	46.12	1.04 [1.03,1.05]	<0.001
Weight (per 5kg increase)	40.91	1.05 [1.03,1.07]	<0.001
Smoker (ever vs. never)	33.73	1.30 [1.19,1.42]	<0.001
Age (per 10-year increase)	33.50	1.20 [1.13,1.28]	<0.001
Sex (male vs. female)	23.65	1.28 [1.16,1.41]	<0.001
History of heart failure	21.02	1.22 [1.12,1.33]	<0.001
Baseline AST (per 5 u/L increase)	15.77	1.04 [1.02,1.05]	<0.001





Predictors of Major GI Bleeding	Chi-Square Statistic	HR [95%CI]	P-Value
Hemoglobin level (per 1-g/dL decrease)	181.19	1.28 [1.23,1.32]	<0.001
Antiplatelet use	57.73	1.53 [1.37,1.70]	<0.001
Creatinine clearance (per 5 mL/min decrease)	45.93	1.05 [1.04,1.07]	<0.001
Age (per 10-year increase)	39.55	1.30 [1.20,1.41]	<0.001
History of heart failure	32.32	1.37 [1.23,1.53]	<0.001
Baseline AST (per 5 u/L increase)	30.90	1.05 [1.03,1.07]	<0.001
Weight (per 5kg increase)	26.85	1.05 [1.03,1.07]	<0.001
Smoker (ever vs. never)	20.53	1.30 [1.16,1.48]	<0.001
Sex (male vs. female)	19.00	1.32 [1.16,1.49]	<0.001
History of diabetes	17.30	1.28 [1.13,1.41]	<0.001



Major or CRNM GI bleeding was assessed across ROCKET AF, ARISTOTLE and ENGAGE AF-TIMI 48 in 53,402 patients. Compared to patients without major or CRNM GI bleeding, those with major or CRNM GI bleeding were older (mean age 72.7 vs 70.1 years), more frequently male (67.1% vs 62.3%), and had a higher comorbidity burden as well as higher mean CHA_2DS_2-VASc (4.5 vs 4.1) and HAS-BLED scores (2.8 vs 2.3). There were 2,070 (3.9%) major or CRNM GI bleeding events occurring over a median follow-up of 23.9 months [IQR 14.8-32] and the annualized incidence was 2.20%/year (95% CI 2.11-2.30%/year).

Major GI bleeding was assessed across all four trials in a total of 71,442 patients. Differences in baseline characteristics between patients who experienced major GI bleeding, vs those that did not, demonstrated a similar pattern to that for major or CRNM GI bleeding described above. There were 1,538 major GI bleeding events (2.2%) occurring over a median follow-up of 23.3 months [IQR 14.9-30.8] and the annualized incidence was 1.22%/year (95%CI 1.16-1.29%/year).

The strongest predictors of major or CRNM GI bleeding were baseline hemoglobin level, concomitant antiplatelet therapy, renal impairment, increasing weight, smoking, sex, heart failure and baseline aspartate aminotransferase level (AST). These predictors were similar for major GI bleeding, and diabetes was additionally identified as an independent predictor of bleeding.

CONCLUSION

Modifiable (including antiplatelet therapy) and non-modifiable risk factors predict increased risk of GI bleeding in patients with AF on oral anticoagulation for stroke prevention.

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The ARISTOTLE trial was funded by Bristol-Myers Squibb and Pfizer, and coordinated by the Duke Clinical Research Institute, Durham, NC, USA and Uppsala Clinical Research Center, Uppsala, Sweden.

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DISCLOSURE

The presenting author, Dr Reddy, has no relevant disclosures or conflicts of interest.

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