Factor XI Inhibition with Abelacimab in Atrial Fibrillation Across the Spectrum of Bleeding Risk

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BACKGROUND

- Bleeding is a common complication of antithrombotic therapy for atrial fibrillation (AF), often resulting in cessation of therapy or undertreatment of patients at risk for thromboembolism.
- Abelacimab is a novel factor XI inhibitor which substantially reduced the risk of major and clinically relevant non-major (CRNM) bleeding relative to rivaroxaban among patients with AF in AZALEA-TIMI 71.
- We sought to assess whether the safety benefit of abelacimab varies by patient-specific bleeding risk.

METHODS

- AZALEA-TIMI 71 randomized 1,287 patients with AF and moderate-high risk for stroke 1:1:1 to abelacimab (150 or 90 mg SC monthly) or rivaroxaban 20 mg PO daily (15 mg for CrCl ≤50 mL/min).
  - ➢ Individual abelacimab doses pooled for this analysis.
- Bleeding risk was examined using the DOAC score (**Table**), a validated risk score designed to predict DOAC-specific bleeding risk, as well as the HAS-BLED score.
  - ➢ DOAC and HAS-BLED scores were categorized by previously established thresholds.
- Primary outcome = major/CRNM bleeding, adjudicated by CEC blinded to treatment assignment and assessed in the on-treatment population.
- Cox Proportional Hazards model was used to examine the effect of abelacimab vs. rivaroxaban with interaction term for (treatment allocation)*(bleeding risk category).

Table: DOAC Score Variables and Weighting

DOAC Score Variable	Points
Age, years	
65-69	+2
70-74	+3
75-79	+4
≥80	+5
CrCl, mL/min	
30-60	+1
<30	+2
Underweight (BMI < 18.5 kg/m²)	+1
Prior Stroke/Systemic Embolism/TIA	+1
Diabetes	+1
Hypertension	+1
Antiplatelet use	
Aspirin	+2
DAPT	+3
NSAID use	+1
History of bleeding	+3
Liver disease	+2

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Figure 1: Distribution of DOAC Score

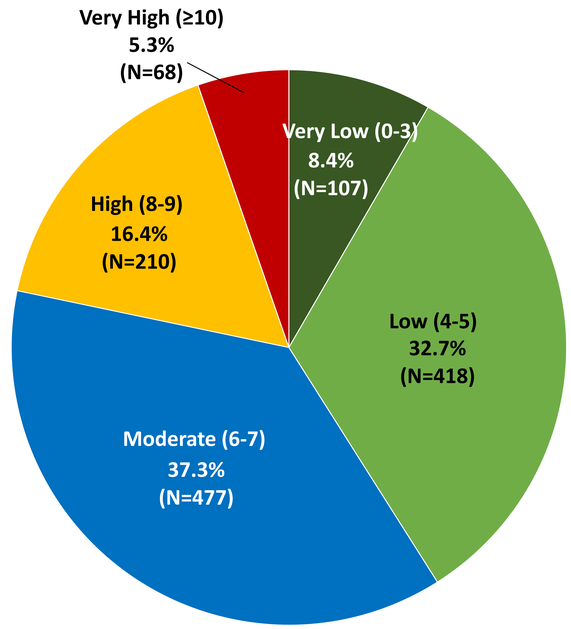
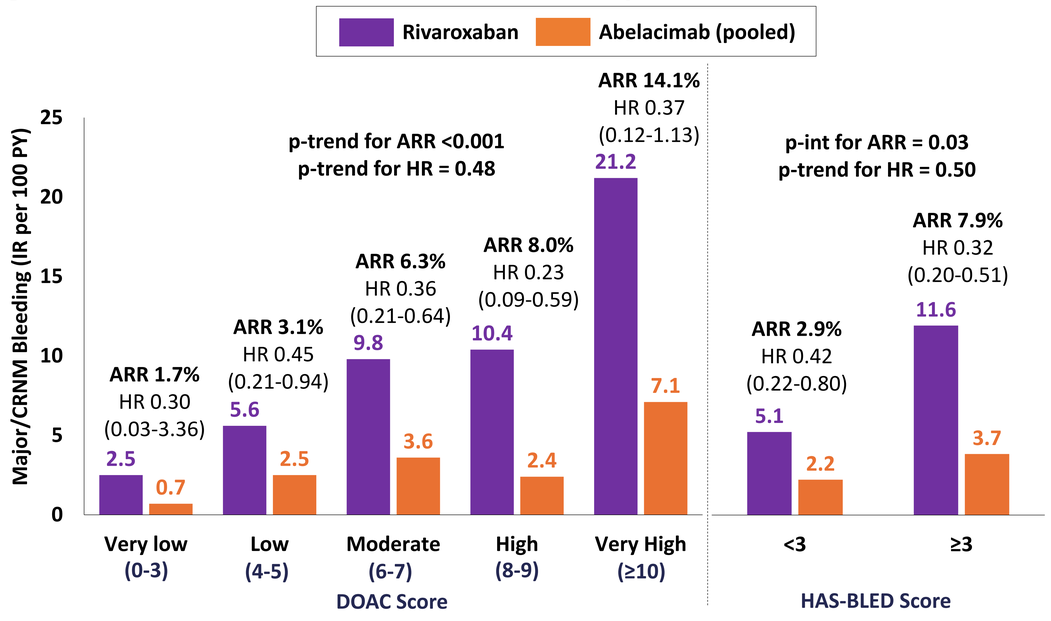


Figure 2: Treatment Effect of Abelacimab vs. Rivaroxaban by DOAC and HAS-BLED Scores



RESULTS

- Among 1,280 patients, 755 (59.0%) were categorized as having at least moderate bleeding risk (≥6 points) by the DOAC score (**Fig 1**). A total of 643 (50.2%) patients were categorized as high bleeding risk by the HAS-BLED score (HAS-BLED ≥ 3).
- Assessed by the DOAC score, rates of major/CRNM bleeding in the rivaroxaban arm ↑ stepwise across risk categories (**Fig 2**).
  - ➢ Abelacimab consistently ↓ rates of bleeding vs. rivaroxaban across risk categories (p-trend for HR = 0.48), with ↑ ARR for those at greater bleeding risk (p-trend for ARR <0.001) (**Fig 2**)
- In the rivaroxaban arm, those with a HAS-BLED ≥3 had a ~2-fold ↑ rate of major/CRNM bleeding vs. those with a HAS-BLED score <3 (**Fig 2**).
  - ➢ Abelacimab consistently ↓ rates of bleeding vs. rivaroxaban irrespective of HAS-BLED (p-int for HR = 0.50), w/ ↑ ARR in those w/ higher HAS-BLED (p-int for ARR= 0.03) (**Fig 2**).

CONCLUSIONS

- In patients with AF, abelacimab reduced rates of bleeding relative to rivaroxaban across the spectrum of bleeding risk, with greater absolute safety benefit in those at higher bleeding risk.
- Emerging factor XI inhibitor therapies may be especially attractive for pts with AF at high bleeding risk.

DISCLOSURE OF RELATIONSHIPS: AZALEA-TIMI 71 was funded by Anthos Therapeutics. SMP, RPG, DAM, ELG, MSS and CTR are members of the TIMI Study Group which has received institutional grant support from Abbott, Abiomed, Inc., Amgen, Anthos Therapeutics, ARCA Biopharma, Inc., AstraZeneca, Boehringer Ingelheim, Daiichi-Sankyo, Ionis Pharmaceuticals, Inc., Janssen Research and Development, LLC, MedImmune, Merck, Novartis, Pfizer, Regeneron Pharmaceuticals, Inc., Roche, Saghmos Therapeutics, Inc., Softcell Medical Limited, The Medicines Company, Verve Therapeutics, Inc., Zora Biosciences. BH, SP and DB are employees of Anthos Therapeutics.