Guiding iterative decision-making in anticoagulant dosing including patient preferences of stroke vs bleeding avoidance: A Bayesian Machine Learning model trained on the ENGAGE AF-TIMI 48 trial

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Disclosures

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Background

- We conduct trials and draw inferences from / about populations
- We treat individual patients, however, who have innumerable combinations of subgroups with second and higher order interactions (which can be modeled with ML/AI)
- We see patients in clinic and iteratively reassess their risk moving forward based upon the presence or absence of events (including multiple events) & their tolerability of a drug / device (eg a patient who has not bled is at a lower risk of bleeding moving forward)
- We should take into account individual patient preferences (not population preferences) with respect to ischemic / bleeding outcomes and side effects
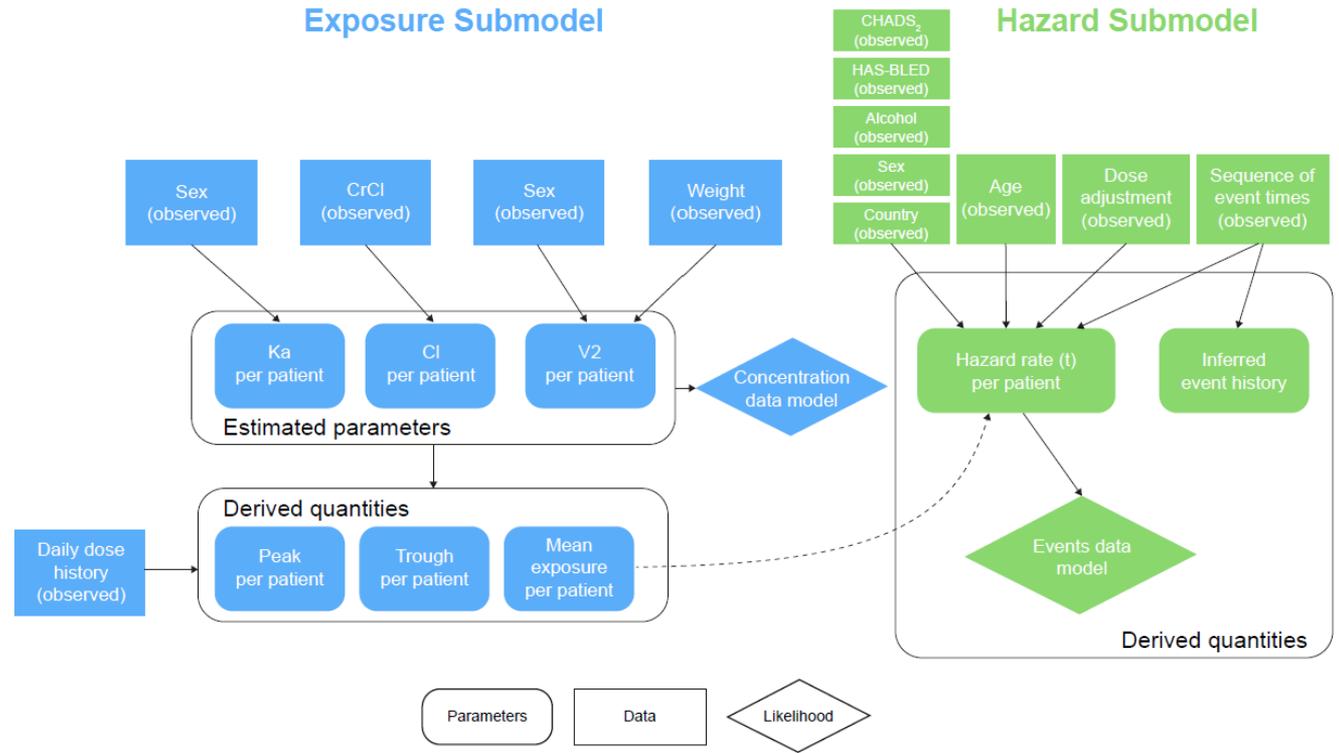
Background/Objective

- Anticoagulation in atrial fibrillation often relies on a single dose, does not consider changes in patient risk during chronic therapy, and does not incorporate patient preferences for risks of stroke, bleeding and death.
- Bayesian machine learning (ML) could improve longitudinal risk prediction and patient-centric care, enabling shared decision making.

Objective: We developed a Bayesian ML model (Adele*) to guide individualized long-term dosing accounting for patient preferences and intercurrent events.

*Adele was named in honor of Myra Adele Logan, the pioneering African American surgeon who was the first woman to perform successful open-heart surgery.

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Methods

Adele is a Bayesian competing-risk, multistate hazard model, developed in 5,380 edoxaban-treated patients with their pharmacokinetic (PK) data from the ENGAGE AF-TIMI 48 trial (NCT00781391)[1-7]

Methods

To demonstrate individual patient predictions, we selected 2 patients from the ENGAGE AF-TIMI 48 trial to illustrate the utility of Adele.

Adele's Applications

#1: Predicting hazards of subsequent events (3-year)
- Conditional on an observed event at 9 months (ICH or an IS)
- Cumulative hazards were estimated by generating more than 50,000 event sequences for each patient

#2: Cumulative weighted event rates (3-year) according to hypothetical patient preferences
- Predict optimal dosing across three edoxaban doses (60mg, 30mg, 15mg) based on patient characteristics and hypothetical patient outcome preferences (e.g., to either avoid CV death, avoid disability, avoid MB, or avoid IS/ICH)
- Outcomes were differentially weighted according to a hypothetical patient's preference

Patient Examples

80-year-old female with persistent AF (Patient A)
- body weight: 52 kg
- CrCl: 42 mL/min
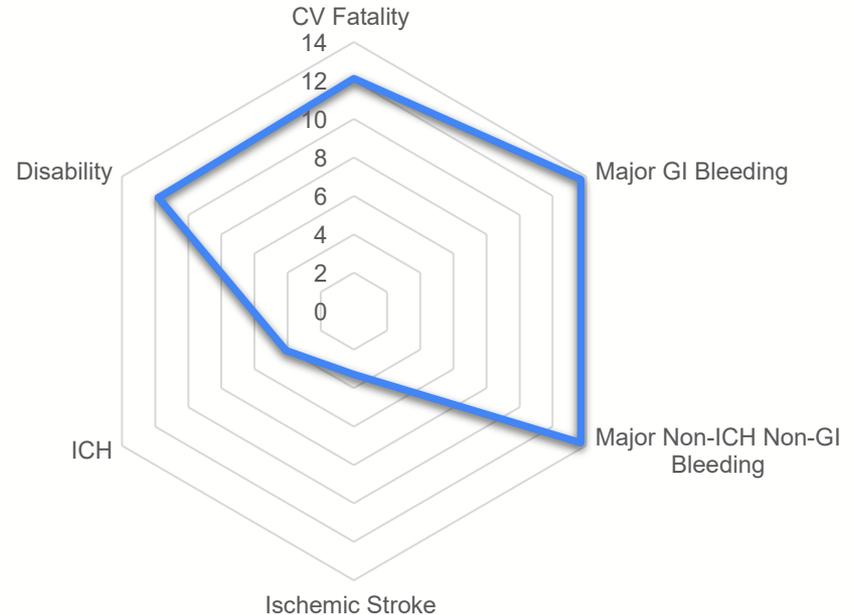- modified HAS-BLED score: 2
- CHADS2 score: 3

72-year-old male with permanent AF (Patient B)
- body weight: 80 kg
- CrCl: 73 mL/min
- modified HAS-BLED score: 2
- CHADS2 score: 4

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Results

Model Performance: Adele outperformed standard Kaplan-Meier estimators across all clinical events, improving 3-year prediction (concordance-index) in the test sample.

- **CV fatality: +12.1%**
- **Disability: +11.8%**
- **Major GI bleeding: +13.7%**
- **Major non-ICH non-GI bleeding: +13.7%**
- **Ischemic stroke: +3.3%**
- **ICH: +4.1%**

% Improvement vs Kaplan-Meier

CV, cardiovascular; GI, gastrointestinal; ICH, intracranial hemorrhage; IS, ischemic stroke; MB, major bleeding.

Results

Predicting hazards of subsequent events (3-year)
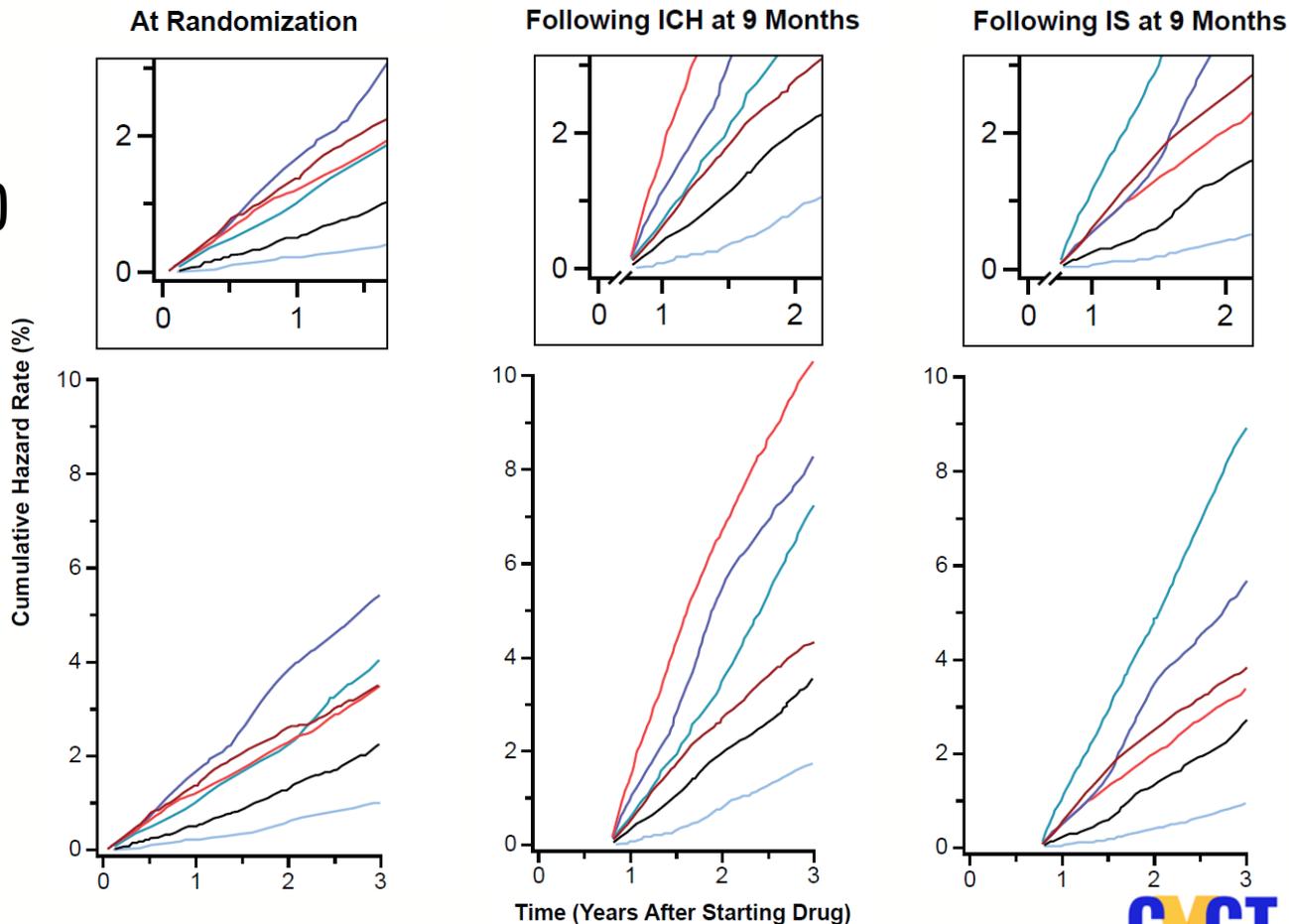
Patient A:

At randomization:
- IS represented the highest baseline risk of ~5% over three years

Following ICH (at 9 months):
- Major GI bleeding emerged as the highest risk, reaching ~10%

Following IS (at 9 months):
- Disability became the predominant risk, peaking at ~8%-9%

GI, gastrointestinal; ICH, intracranial hemorrhage; IS, ischemic stroke.

Results

Predicting hazards of subsequent events (3-year)
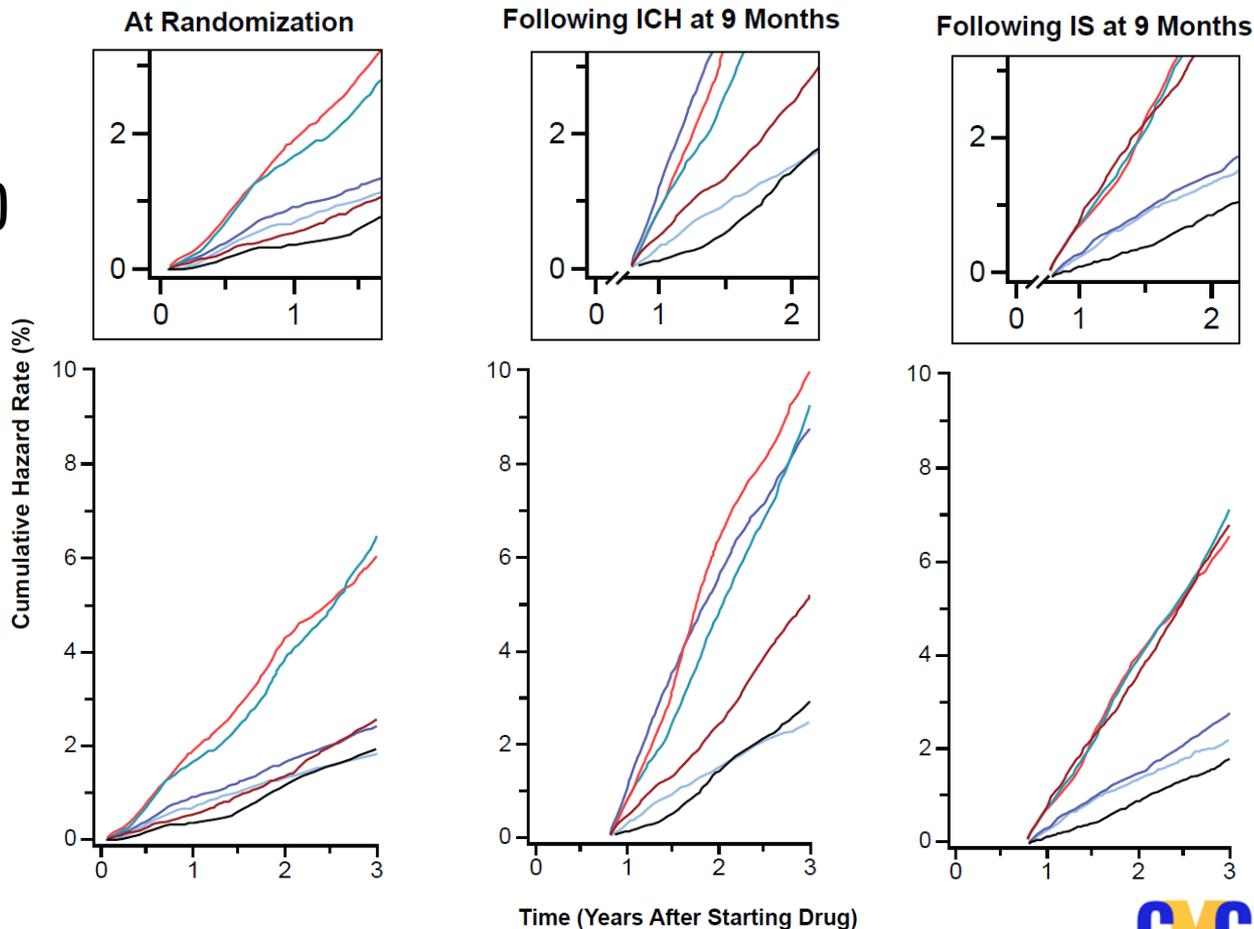
Patient B:

At randomization:
- Major GI bleeding and disability were the highest baseline risks (~6%)
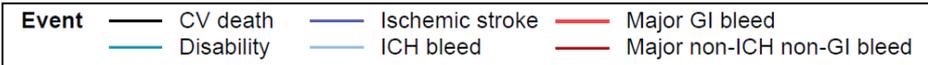
Following ICH (at 9 months):
- Major GI bleeding and disability emerged as the highest risks (~9-10%)

Following IS (at 9 months):
- Major GI bleeding, disability, and major non-ICH non-GI bleeding became the predominant risks (6.5-7%)

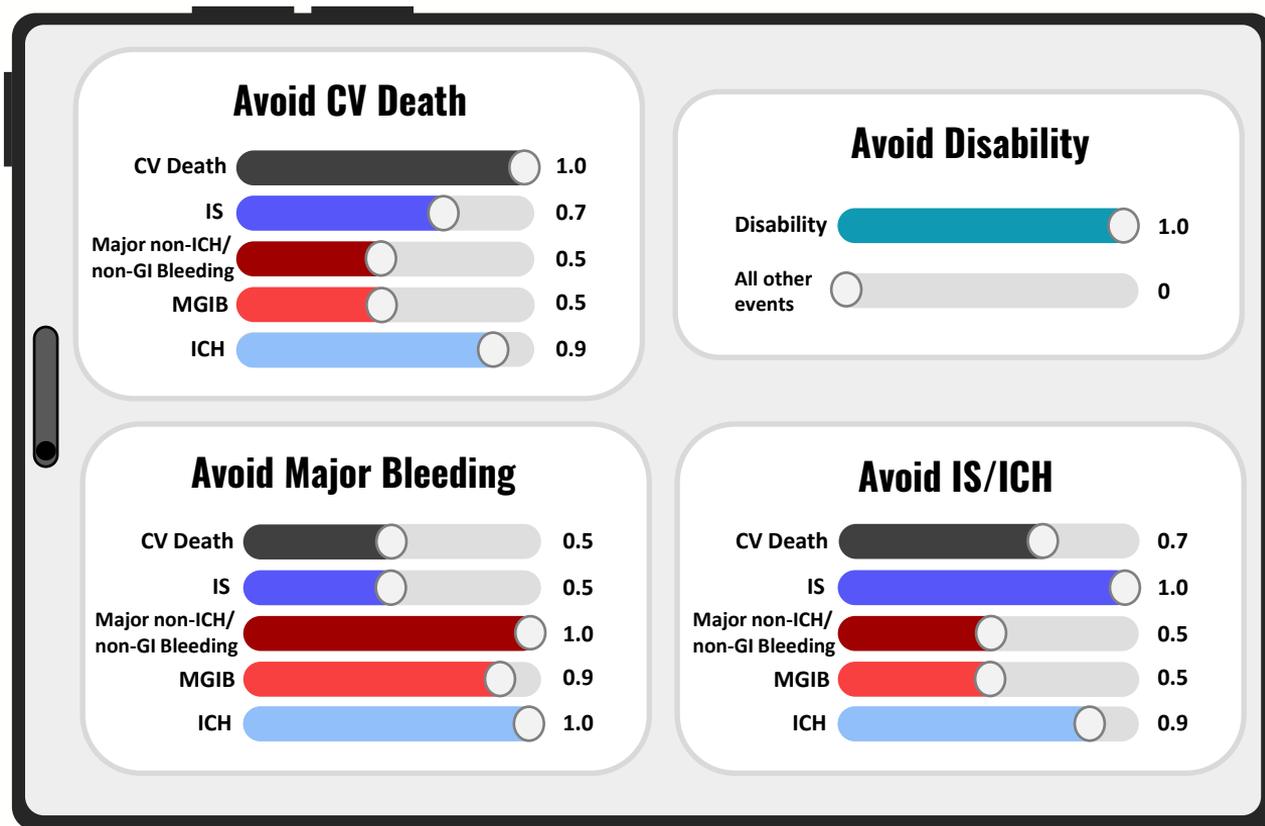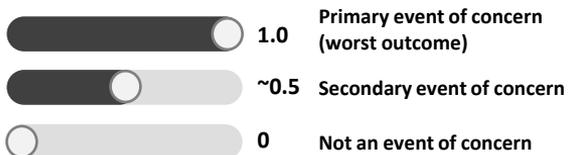GI, gastrointestinal; ICH, intracranial hemorrhage; IS, ischemic stroke.
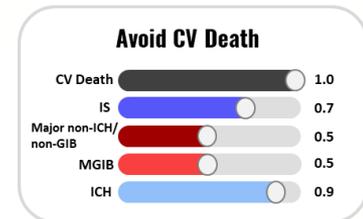

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Methods

Patient Preference: Weighting Events

Interpreting Hypothetical Patient Weighting

slider at 1.0	**1.0**	Primary event of concern (worst outcome)
slider at ~0.5	**~0.5**	Secondary event of concern
slider at 0	**0**	Not an event of concern

Avoid CV Death

CV Death	1.0
IS	0.7
Major non-ICH/non-GI Bleeding	0.5
MGIB	0.5
ICH	0.9

Avoid Disability

Disability	1.0
All other events	0

Avoid Major Bleeding

CV Death	0.5
IS	0.5
Major non-ICH/non-GI Bleeding	1.0
MGIB	0.9
ICH	1.0

Avoid IS/ICH

CV Death	0.7
IS	1.0
Major non-ICH/non-GI Bleeding	0.5
MGIB	0.5
ICH	0.9

CV, cardiovascular; GI, gastrointestinal; ICH, intracranial hemorrhage; IS, ischemic stroke; MGIB, major gastrointestinal bleeding.

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Results – Avoid CV Death

Cumulative weighted event rates (3-year) according to hypothetical patient preferences

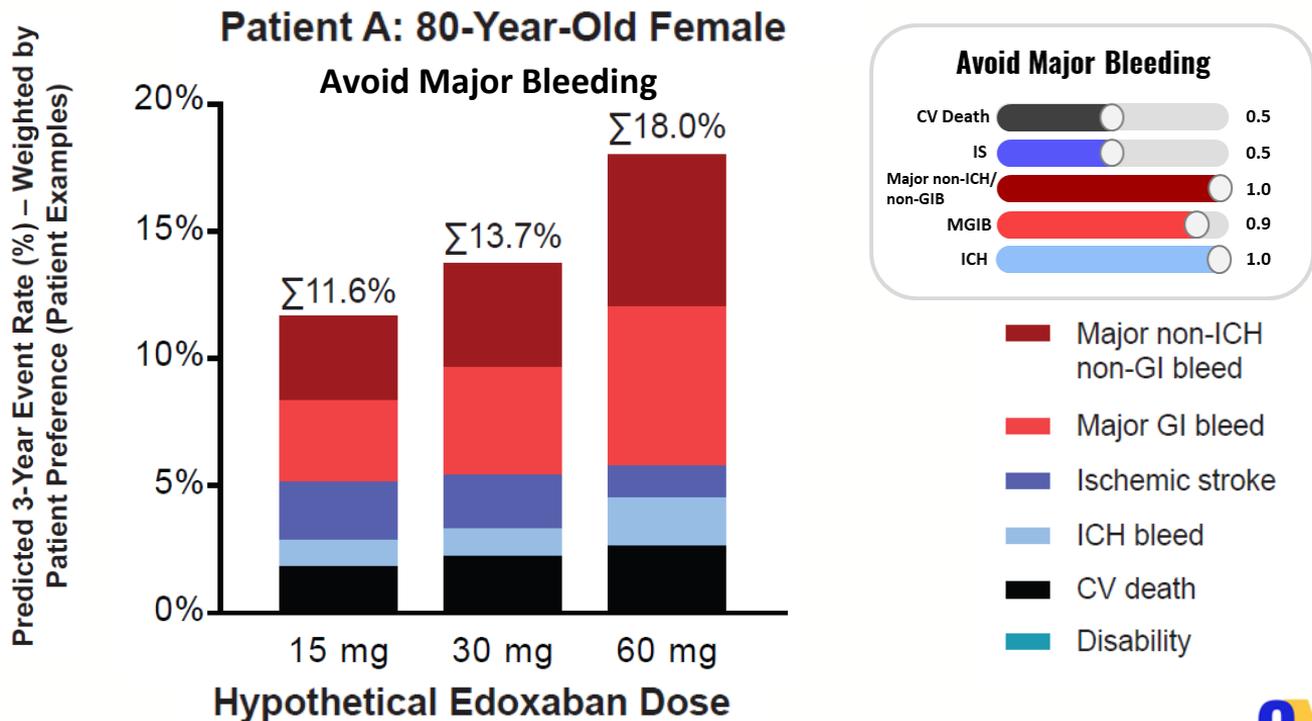CV, cardiovascular; GI, gastrointestinal; ICH, intracranial hemorrhage; IS, ischemic stroke; MGIB, major gastrointestinal bleeding.

Results – Avoid Disability

Cumulative weighted event rates (3-year) according to hypothetical patient preferences

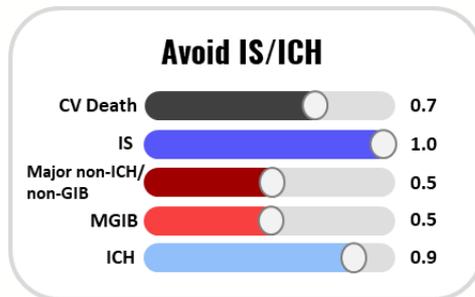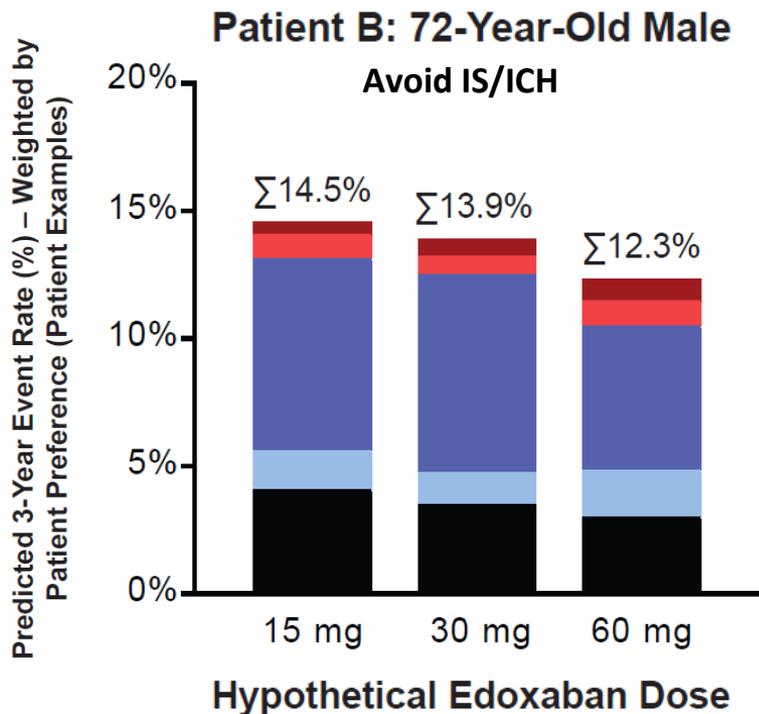CV, cardiovascular; GI, gastrointestinal; ICH, intracranial hemorrhage; IS, ischemic stroke; MGIB, major gastrointestinal bleeding.

Results – Avoid Major Bleeding (Patient A)

Cumulative weighted event rates (3-year) according to hypothetical patient preferences

Patient A: 80-Year-Old Female
Avoid Major Bleeding

Avoid Major Bleeding
- CV Death — 0.5
- IS — 0.5
- Major non-ICH/non-GIB — 1.0
- MGIB — 0.9
- ICH — 1.0

Legend:
- Major non-ICH non-GI bleed
- Major GI bleed
- Ischemic stroke
- ICH bleed
- CV death
- Disability

Y-axis: Predicted 3-Year Event Rate (%) – Weighted by Patient Preference (Patient Examples)

X-axis: Hypothetical Edoxaban Dose (15 mg, 30 mg, 60 mg)

∑11.6% ∑13.7% ∑18.0%

CV, cardiovascular; GI, gastrointestinal; ICH, intracranial hemorrhage; IS, ischemic stroke; MGIB, major gastrointestinal bleeding.

Results – Avoid IS/ICH (Patient B)

Cumulative weighted event rates (3-year) according to hypothetical patient preferences

CV, cardiovascular; GI, gastrointestinal; ICH, intracranial hemorrhage; IS, ischemic stroke; MGIB, major gastrointestinal bleeding.

Conclusions

- Adele represents a state-of-the-art Bayesian ML framework, leveraging clinical factors and PK data, to enable longitudinally adaptive, preference-weighted, event predictions, and thus patient centric care.

This paradigm supports iterative, shared decision-making, offering a path toward potentially safer and more effective anticoagulation therapy and should be applicable to other chronic treatments.

Disclaimer: Approved edoxaban doses vary throughout the world; e.g., edoxaban 15 mg is approved in Japan, China, and other Asian countries, but not in Europe or the United States; prescribing practices should adhere to the local approved label.

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