Efficacia degli inibitori del fattore Xa nella prevenzione dell'ictus ischemico in assenza di storia di fibrillazione atriale

Background

- Oral factor Xa (fXa) inhibitors are direct-acting anticoagulants that reduce the risk of ischemic stroke for patients with atrial fibrillation, but their effect on ischemic stroke in patients without a history of AF is less clear.
- Results from RCTs appear to be conflicting: rivaroxaban given in a low dose reduced ischemic stroke compared with placebo when given in addition to aspirin in the COMPASS trial, but a higher rivaroxaban dosage did not reduce ischemic stroke compared with aspirin in the New Approach Rivaroxaban Inhibition of Factor Xa in a Global Trial versus ASA to Prevent Embolism in Embolic Stroke of Undetermined Source (NAVIGATE ESUS) trial.
- Contributing to the uncertainties are testing of different specific oral fXa inhibitors in dosages with varying levels of anti-Xa activity involving different patient populations and testing in addition to different background antiplatelet therapies.

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Clinical Research

Are Factor Xa Inhibitors Efficacious for Ischemic Stroke Prevention in Patients Without Atrial Fibrillation? Evidence From Randomized Clinical Trials

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Methods

- The authors reviewed RCTs that tested oral fXa inhibitors that reported ischemic stroke as an outcome with the primary goal of evaluating whether oral fXa inhibitors can potentially prevent ischemic stroke in patients without a history of AF.
- A secondary objective was to assess major bleeding, and particularly intracranial bleeding, associated with oral fXa inhibitors in these trials that would offset any benefits for reduction in ischemic stroke.
- Because different oral fXa inhibitors were tested in different dosages and in different patient populations, a meta-analysis leading to point estimates of aggregate treatment effects was considered to be potentially misleading and was not undertaken.

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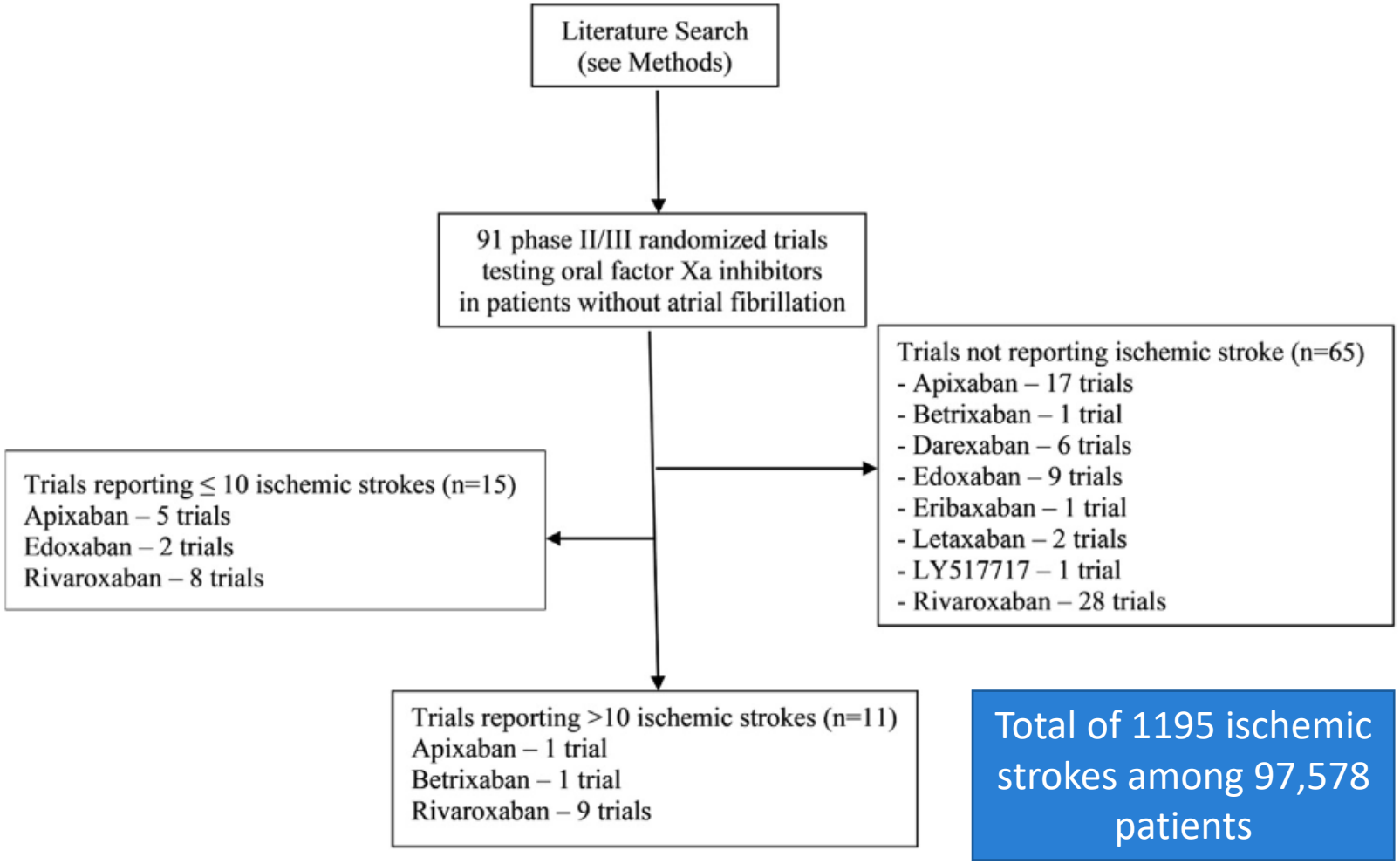
Literature search



Total of 1195 ischemic strokes among 97,578 patients

- Eight trials did not specifically exclude participants with AF, but a requirement for anticoagulation was an exclusion criterion; the number of participants with AF was usually not reported
- A single trial (NAVIGATE ESUS) had ischemic stroke as the major component of the primary outcome.

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RCT that tested oral fXa inhibitors and reported ischemic stroke

Trial	Trial population	N	Mean age, years	Randomized treatment arms	Comments: follow-up times; concomitant antiplatelet use; exclusion of AF
Apixaban					
APPRAISE-2[8]	ACS and ≥ 2 risk factors	7392	67	Apixaban 5 mg bid, placebo	Median, 241 days (IQR, 131-352); 97% ASA, 81% thienopyridine at entry; need for anticoagulation an exclusion; AF NR
Betrixaban					
APEX[9]	Hospitalization for acute medical illness	7432	76	Betrixaban 80 mg/d for 36 days, enoxaparin 40 mg/d for 9 days	Mean, approximately 42 days, median treatment duration 36 days (IQR, 34-39) for betrixaban and 9 days (IQR, 7-13) for enoxaparin; 49% antiplatelet (92% was ASA) in each arm[24]; AF not specifically excluded unless requiring anticoagulation, AF frequency NR except 26% of participants with heart failure had AF[23]

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RCT that tested oral fXa inhibitors and reported ischemic stroke

Rivaroxaban					
ATLAS ACS 2[19]	ACS	15342	62	Rivaroxaban 2.5 mg bid, rivaroxaban 5 mg bid, placebo	Mean, 13.1 months; 99% ASA, 93% thienopyridine; AF excluded except those younger than 60 years with lone AF
COMMANDER-HF[16]	Chronic HF and CAD, recent worsening of HF	5022	66	Rivaroxaban 2.5 mg bid, placebo	Median, 21 months (IQR, 13-33); 93% ASA, 35% DAPT; AF excluded
COMPASS[4,10]	Chronic coronary or peripheral atherosclerotic vascular disease	27,395	68	Rivaroxaban 5 mg bid, rivaroxaban 2.5 mg bid with ASA 100 mg/d, ASA 100 mg/d	Mean, 23 months; AF not specifically excluded unless requiring anticoagulation
GALILEO[11]	Transcatheter aortic valve replacement	1644	81	Rivaroxaban 10 mg/d with ASA 75-100 mg/d for 3 months, ASA 75-100 mg/d with CPG 75 mg/d for 3 months	Median, 17 months (IQR, 13-21): ASA and CPG given for 3 months; indication for chronic anticoagulation an exclusion, 11% identified as developing AF during follow-up
GEMINI-ACS-1[12]	ACS	3037	62	Rivaroxaban 2.5 mg bid, ASA 100 mg/d	Median, 291 days (IQR, 239-354); additional CPG/ticagrelor required; need for anticoagulation an exclusion, AF frequency NR
MAGELLAN Subgroup[13]	Post-hospital discharge for medical illness	6716	69	Rivaroxaban 10 mg/d, placebo	Approximately 25 days; AF frequency 13%; antiplatelet use NR
MARINER Subgroup[14]	Post-hospital discharge for medical illness	9821	68	Rivaroxaban 10 mg/d, placebo	45 Days; indication for anticoagulation an exclusion, AF frequency 3%; 50% receiving ASA
NAVIGATE ESUS[5]	Recent embolic cryptogenic stroke	7213	67	Rivaroxaban 15 mg/d, ASA 100 mg/d	Median, 11 months (IQR, 5-17); mandatory cardiac rhythm monitoring required before randomization to exclude covert AF
VOYAGER PAD[15]	PVD after revascularization	6564	67	Rivaroxaban 2.5 mg bid, placebo	Median, 28 months (IQR, 22-34); all received ASA 100 mg/d; AF not specifically excluded unless requiring anticoagulation; AF frequency NR

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Results-ischemic stroke

- In 7 trials with placebo comparisons, numerically fewer ischemic strokes occurred among those assigned factor Xa inhibitors in 7 of 8 randomized comparisons (range of hazard ratios [HRs], 0.89-0.51).
- Statistically significant reductions in 2 trials that compared rivaroxaban 2.5 mg twice daily vs placebo on a background of aspirin in patients with cardiovascular disease:
  - COMPASS (HR, 0.51; 95% confidence interval [CI], 0.38-0.68)
  - COMMANDER-HF (HR, 0.64; 95% CI, 0.43-0.95)
- Compared with aspirin in 4 trials, oral factor Xa inhibitors were associated with fewer ischemic strokes in 2, with statistically significant reduction in 1 (rivaroxaban 5 mg twice daily in COMPASS; HR, 0.69; 95% CI, 0.53-0.90).

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Results- major bleeding

- **Major bleeding** was increased by oral factor Xa inhibitors in all 7 placebo-controlled trials (HR range, 1.42-4.08), with statistically significant increases reported in 5 trials, and in all 4 aspirin-controlled trials (all statistically significant increases; HR range, 1.52-2.72).
- **Symptomatic intracranial hemorrhages** were reported in 228 participants in 9 trials, comprising 16% of major bleeds, and were 20% as frequent as ischemic strokes.
- Intracranial hemorrhages were numerically increased in those assigned fXa inhibitors in 4 of 6 placebo-controlled comparisons and in 2 of 4 aspirin-controlled comparisons.
- Considering absolute rates of ischemic stroke and intracranial hemorrhage, absolute increases in intracranial hemorrhage offset absolute reductions in ischemic stroke in the 2 placebo-controlled RCTs that enrolled patients with acute coronary syndromes and substantially offset the reduction in ischemic stroke in 1 aspirin-controlled trial.

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Randomized comparisons of the effects of fXa inhibitors on ischemic stroke and intracranial hemorrhage

Trial	Study cohort	Ischemic stroke			Symptomatic intracranial hemorrhage		
		Anti-fXa drug n/N patients	Control n/N patients	Hazard ratio (95% CI)	Anti-fXa drug n/N patients	Control n/N patients	Hazard ratio (95% CI)
Placebo-controlled trials							
APPRAISE-2[8]	ACS	Apixaban 5 mg bid 23/3705	Placebo 34/3687	0.68 (0.40-1.15)	Apixaban 5 mg bid 12/3673	Placebo 3/3642	4.06 (1.15-14.4)
ATLAS ACS 2[19]	ACS	Rivaroxaban 2.5 mg bid 30/5114	Placebo 34/5113	0.89 (0.55-1.45)	Rivaroxaban 2.5 mg bid 14/5115	Placebo 5/5125	NR
ATLAS ACS 2[19]	ACS	Rivaroxaban 5 mg bid 35/5115	Placebo 34/5113	1.05 (0.65-1.68)	Rivaroxaban 5 mg bid 18/5110	Placebo 5/5125	NR
COMMANDER-HF[16,18]	Heart failure	Rivaroxaban 2.5 mg bid 41/2507	Placebo 63/2515	0.64 (0.43-0.95)	Rivaroxaban 2.5 mg bid 7†/2507	Placebo 11†/2515	NR
COMPASS[4,10]	Stable CVD	Rivaroxaban 2.5 mg bid 68/9152	Placebo 132/9126	0.51 (0.38-0.68)	Rivaroxaban 2.5 mg bid 28/9152	Placebo 24/9126	1.16 (0.67-2.00)
MAGELLAN Subgroup[13]	Post-hospital VTE	Rivaroxaban 10 mg/d 7/3332	Placebo 12/3384	0.60 (0.23-1.51)	Rivaroxaban 10 mg/d NR	Placebo NR	NR
MARINER Subgroup[14]	Post-hospital VTE	Rivaroxaban 10 mg/d 13/4909	Placebo 24/4913	0.54 (0.28-1.06)	Rivaroxaban 10 mg/d NR	Placebo NR	NR
VOYAGER PAD[15]	Post-revascularization PVD	Rivaroxaban 2.5 mg bid 71/3286	Placebo 82/3278	0.87 (0.63-1.19)	Rivaroxaban 2.5 mg bid 13/3256	Placebo 17/3248	0.78 (0.38-1.61)

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Randomized comparisons of the effects of fXa inhibitors on ischemic stroke and intracranial hemorrhage

Trial	Study cohort	Ischemic stroke: Anti-fXa drug n/N patients	Ischemic stroke: Control n/N patients	Ischemic stroke: Hazard ratio (95% CI)	Symptomatic intracranial hemorrhage: Anti-fXa drug n/N patients	Symptomatic intracranial hemorrhage: Control n/N patients	Symptomatic intracranial hemorrhage: Hazard ratio (95% CI)
ASA-controlled trials							
COMPASS[4,10]	Stable CVD	Rivaroxaban 5 mg bid 91/9117	ASA 100 mg/d 132/9126	0.69 (0.53-0.90)	Rivaroxaban 5 mg bid 43/9117	ASA 100 mg/d 24/9126	1.80 (1.09-2.96)
GALILEO[11]	Transcatheter aortic valve replacement	Rivaroxaban 10 mg/d and ASA for 3 months 28/826	ASA 75-100 mg/d and CPG for 3 months 22/818	1.28 (0.73-2.23)	Rivaroxaban 10 mg/d and ASA for 3 months 2†/826	ASA 75-100 mg/d and CPG for 3 months 3†/818	NR
GEMINI-ACS-1[12]	ACS	Rivaroxaban 2.5 mg bid 7/1519	ASA 100 mg/d 12/1518	0.58 (0.23-1.48)	Rivaroxaban 2.5 mg bid 1/1519	ASA 100 mg/d 0/1518	NR
NAVIGATE ESUS[5]	Recent stroke	Rivaroxaban 15 mg/d 158/3609	ASA 100 mg/d 156/3604	1.01 (0.81-1.26)	Rivaroxaban 15 mg/d 20/3609	ASA 100 mg/d 5/3604	4.02 (1.51-10.7)
Trials with other comparator groups							
APEX[9]	Hospitalized with VTE risk	Betrixaban 80 mg/d for 36 days 18/3716	Enoxaparin 40 mg/d for 9 days, placebo 34/3716	0.53 (0.30-0.94)‡	Betrixaban 80 mg/d for 36 days 1/3716	Enoxaparin 40 mg/d for 9 days, placebo 1/3716	1.00 (0.06-16)‡
ATLAS ACS 2[19]	ACS	Rivaroxaban 2.5 mg bid 30/5114	Rivaroxaban 5 mg bid 35/5115	NR	Rivaroxaban 2.5 mg bid 14/5115	Rivaroxaban 5 mg bid 18/5110	NR
COMPASS[4,10]	Stable CVD	Rivaroxaban 2.5 mg bid and ASA 100 mg/d 68/9152	Rivaroxaban 5 mg bid 91/9117	NR	Rivaroxaban 2.5 mg bid and ASA 100 mg/d 28/9152	Rivaroxaban 5 mg bid 43/9117	NR

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Effects of oral fXa inhibitors on major bleeding

Trial	All major bleeding[†] Anti-fXa drug N/n patients	Control N/n patients	Hazard ratio (95% CI)[‡]
Placebo-controlled trials			
APPRAISE-2[8]	Apixaban 5 mg bid 98/3673	Placebo 40/3642	2.48 (1.72-3.58)
ATLAS ACS 2[19,†]	Rivaroxaban 2.5 mg bid 65/5115	Placebo 19/5125	NR
ATLAS ACS 2[19,†]	Rivaroxaban 5 mg bid 82/5110	Placebo 19/5125	NR
COMMANDER-HF[16]	Rivaroxaban 2.5 mg bid 82/2499	Placebo 50/2509	1.68 (1.18-2.39)
COMPASS[4,10]	Rivaroxaban 2.5 mg bid 206/9152	Placebo 116/9126	1.78 (1.41-2.23)
MAGELLAN Subgroup[13,†]	Rivaroxaban 10 mg/d 4/3332	Placebo 1/3384	4.08 (0.46-36)
MARINER Subgroup[26]	Rivaroxaban 10 mg/d 13/4890	Placebo 9/4890	1.44 (0.62-3.37)
VOYAGER PAD[15]	Rivaroxaban 2.5 mg bid 140/3256	Placebo 100/3248	1.42 (1.10-1.84)
ASA-controlled trials			
COMPASS[4,10]	Rivaroxaban 5 mg bid 175/9117	ASA 100 mg/d 116/9126	1.52 (1.20-1.92)
GALILEO[11]	Rivaroxaban 10 mg/d and ASA 7-100 mg/d for 3 months 49/826	ASA 75-100 mg/d and CPG for 3 months 30/818	1.66 (1.05-2.62)
GEMINI-ACS-1[12]	Rivaroxaban 2.5 mg bid 31/1519	ASA 100 mg/d 17/1518	1.83 (1.01-3.31)
NAVIGATE ESUS[5]	Rivaroxaban 15 mg/d 62/3609	ASA 100 mg/d 23/3604	2.72 (1.68-4.39)
Trials with other comparator groups			
APEX[9]	Betrixaban 80 mg/d for 36 days 25/3716	Enoxaparin 40 mg/d for 9 days, placebo 21/3716	1.19 (0.67-2.12)[§]
ATLAS ACS 2[19,†]	Rivaroxaban 2.5 mg bid 65/5115	Rivaroxaban 5 mg bid 82/5110	NR
COMPASS[4,10]	Rivaroxaban 5 mg bid 175/9117	Rivaroxaban 2.5 mg bid and ASA 206/9152	NR

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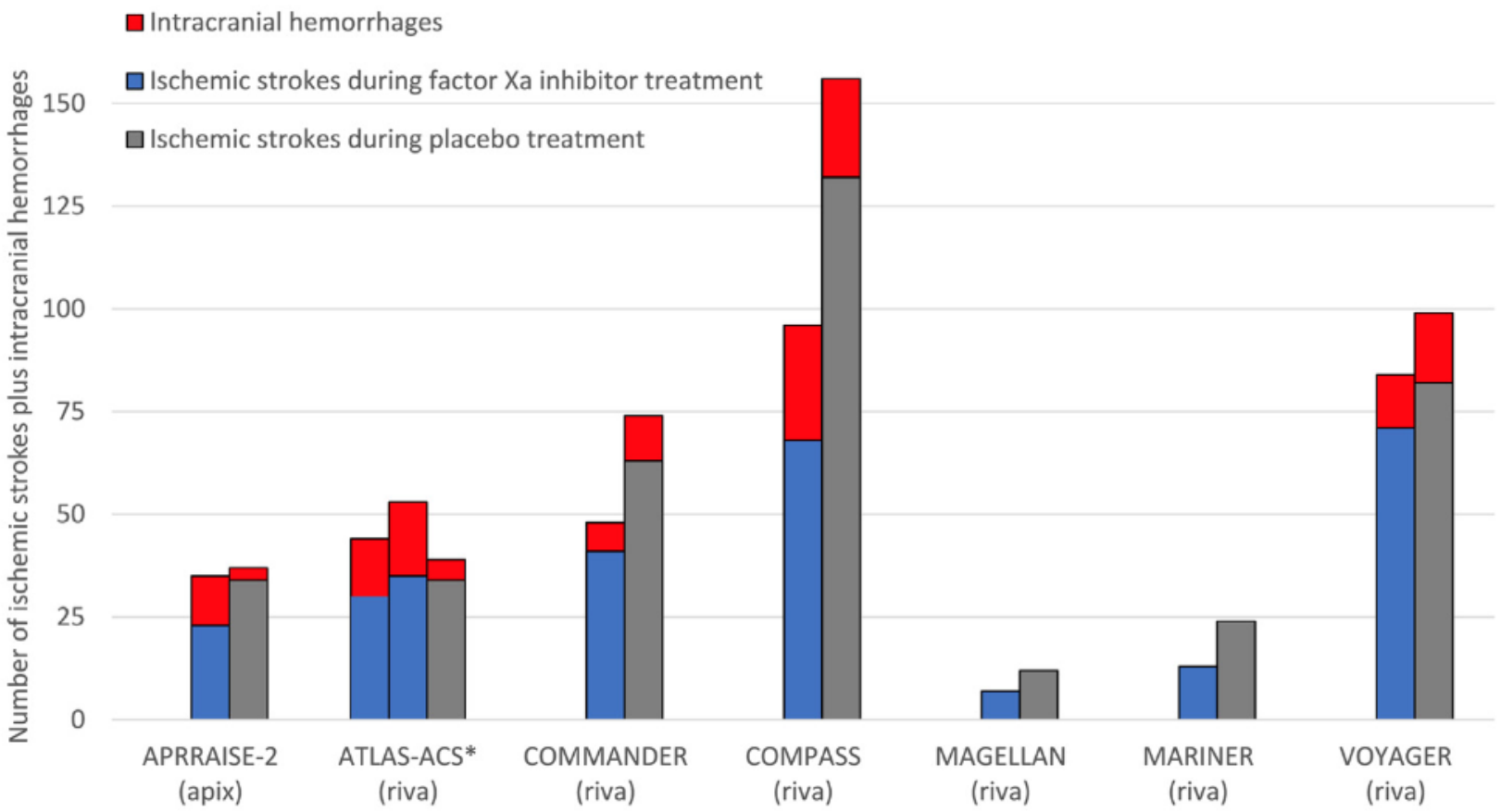
Number of ischemic strokes and intracranial hemorrhages

PLACEBO-CONTROLLED TRIALS



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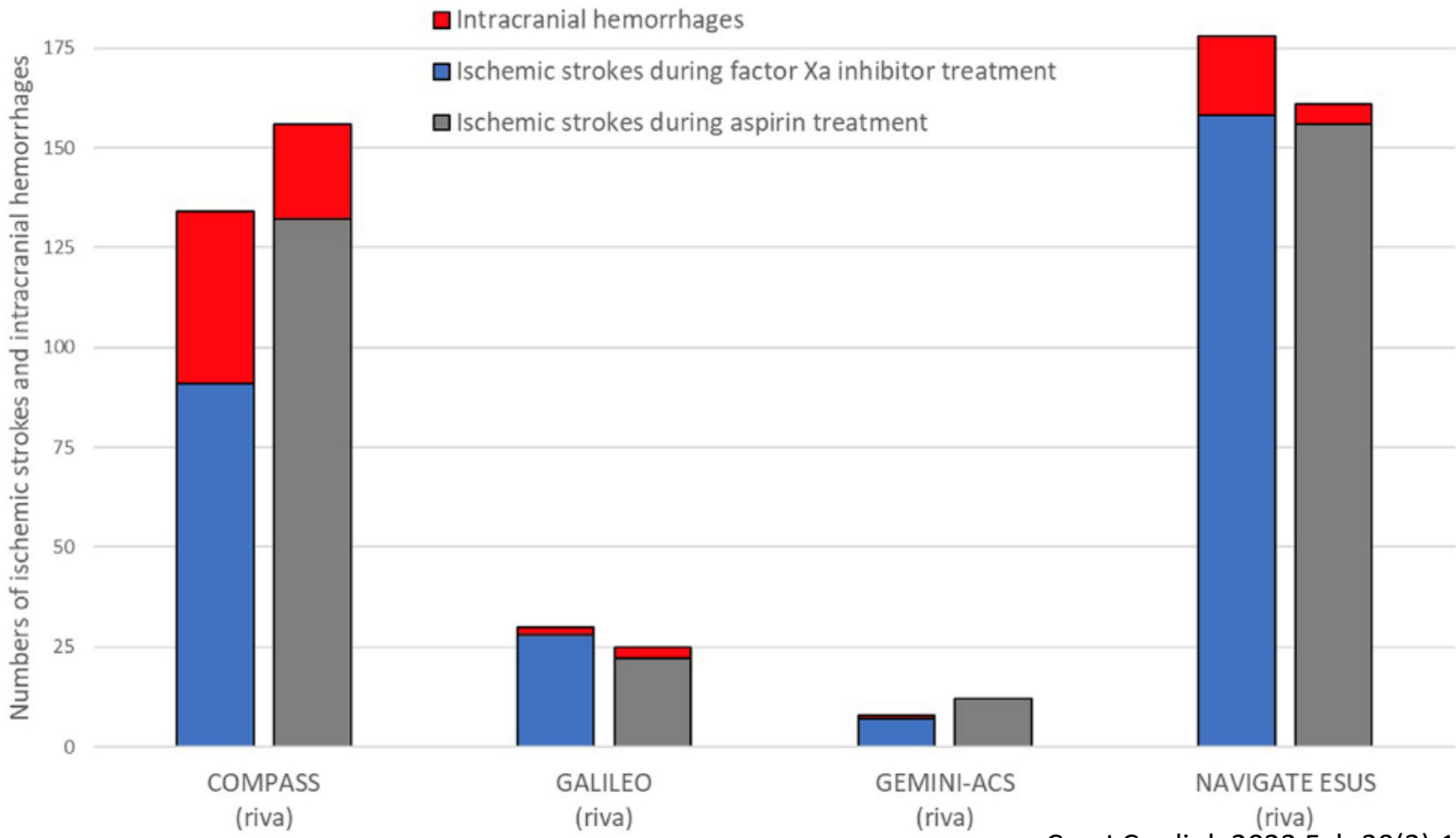
Number of ischemic strokes and intracranial hemorrhages

ASPIRIN-CONTROLLED TRIALS



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Limitations

- Most RCTs that tested oral fXa inhibitors in patients without AF did not report ischemic stroke or reported ≤ 10 ischemic strokes, precluding meaningful interpretation of effects in individual trials
- No trial had ischemic stroke as the primary study outcome (although several trials included all strokes in the primary outcome composite).
- With the exception of NAVIGATE ESUS, trials mainly involved participants without previous stroke (ie, they assessed primary stroke prevention).
- The effect of oral fXa inhibitors on ischemic stroke in patient cohorts with very low rates of stroke (and consequently few ischemic strokes observed) that were under-represented in these analyses could not be characterized.

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Conclusions

- Oral fXa inhibitors potentially reduce ischemic stroke for patients with no history of AF.
- Heterogeneity of treatment effects precludes a single meaningful estimate of efficacy applicable to unselected patients.
- The strongest evidence was for rivaroxaban 2.5 mg twice daily when given with aspirin in patients with atherosclerotic cardiovascular disease.
- Too few data exist to allow comparison of specific drugs and dosages, effects in different patient populations, and on ischemic stroke subtypes.
- Major bleeding, including intracranial hemorrhage, was consistently increased among patients assigned oral fXa inhibitors.
- In patient populations with low absolute rates of ischemic stroke, increases in major bleeding are likely to negate any benefits of reduction of ischemic stroke.
- Clinical use of oral fXa inhibitors specifically for ischemic stroke prevention in patients without a history of AF must await results of additional RCTs that show efficacy and safety in specific, well defined patient cohorts and that have stroke as the primary outcome.

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