A Randomized Trial Evaluating Clinically Significant Bleeding with Low-Dose Rivaroxaban vs Aspirin, in Addition to P2Y12 inhibition, in ACS

Magnus Ohman MB, on behalf of the GEMINI-ACS-1 Investigators

ACC.17
66th Annual Scientific Session & Expo

GEMINI ACS 1

Beth Israel Deaconess Medical Center

A major teaching hospital of Harvard Medical School

Duke Clinical Research Institute

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Conflict of Interest Disclosure

- Disclosures for Dr Ohman listed on www.dcri.org and for all authors within the manuscript

Trial Conduct

- Academic Coordinating Centers: Duke Clinical Research Institute and Perfuse Study Group, Beth Israel Deaconess, Harvard Medical School
  - Independently performed statistical analysis (Frank Rockhold, PhD and Jennifer White, MS)
  - Event adjudication (Dr Thomas J. Povsic, DCRI—Chair)
- Sponsors: Janssen Research & Development (Dr Alexei Plotnikov) and Bayer AG (Dr Hardi Mundi)
  - Global trial management
- Protocol adherence
  - Total of 1 patient lost to follow-up (0.03% of overall)
  - Median study follow-up: 326 days (25th, 75th%: 284, 383 days)

Background

- Aspirin and dual antiplatelet therapy (aspirin + a P2Y12 inhibitor [DAPT]) have become foundational therapy in ACS, while nearly 10% of patients still suffer a major cardiovascular event during follow-up
- Triple antithrombotic therapy with DAPT + rivaroxaban, a Xa inhibitor, has been shown to reduce cardiovascular events, but with a significantly higher rate of major bleeding complications
- In-vivo thrombosis and bleeding studies have suggested that rivaroxaban with a P2Y12 inhibitor had similar efficacy to DAPT, but with lower risk of bleeding
- These findings, in concert with studies in post-PCI patients with atrial fibrillation (where aspirin was dropped), suggest that dual-pathway therapy with Rivaroxaban and a P2Y12 agent may be a way to enhance overall outcomes in ACS

Inclusion Criteria

- Randomization within 10 days of an ACS event
  - STEMI and Non-STEMI patients required positive biomarkers (troponin or CK-MB) with either ECG changes or thrombotic culprit lesion at cath
  - Unstable angina patients required at least ECG changes, TIMI risk score >4, or revascularization for ACS
- Patient age >18 years
- Patients age <55 years required 1 of 2 enrichment criteria
  - History of diabetes
  - Prior MI

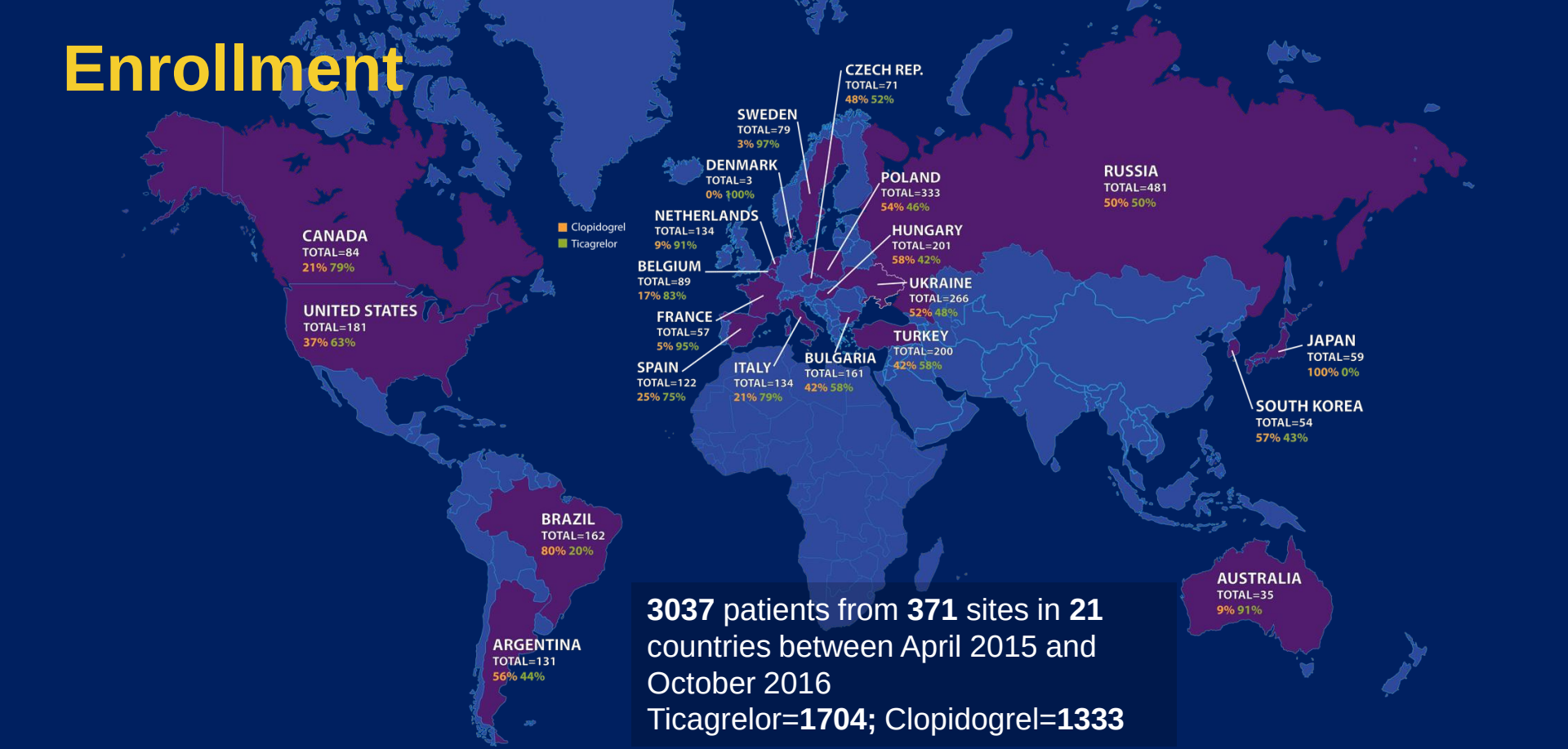
Exclusion Criteria

- History of active bleeding, intracranial bleeding, or significant GI bleeding with 12 months
- Estimated creatinine clearance <20 mL/min
- Use of omeprazole
  - In clopidogrel strata only
- Need for chronic full-dose anticoagulation
- All patients were tested for P2Y12 metabolite status and results were provided to caring physician within 2 weeks of randomization to allow poor clopidogrel metabolizer patients to be switched

Statistical Considerations

- Designed as a phase 2 trial to estimate TIMI non-CABG clinically significant bleeding risk of rivaroxaban compared with aspirin with either clopidogrel or ticagrelor
- Sample size of approximately 3,000 patients
  - Based on estimated bleeding rate of 6.5% at 360 days
  - An estimated upper bound of 95% CI of 2.0 = 170 events
- Intention-to-treat to first event using Cox proportional hazards model
- Exploratory analysis of other bleeding definitions
- Exploratory analysis of composite ischemic endpoint of CV death, MI, stroke, or definitive stent thrombosis

Enrollment



3037 patients from **371** sites in **21** countries between April 2015 and October 2016
Ticagrelor=**1704;** Clopidogrel=**1333**

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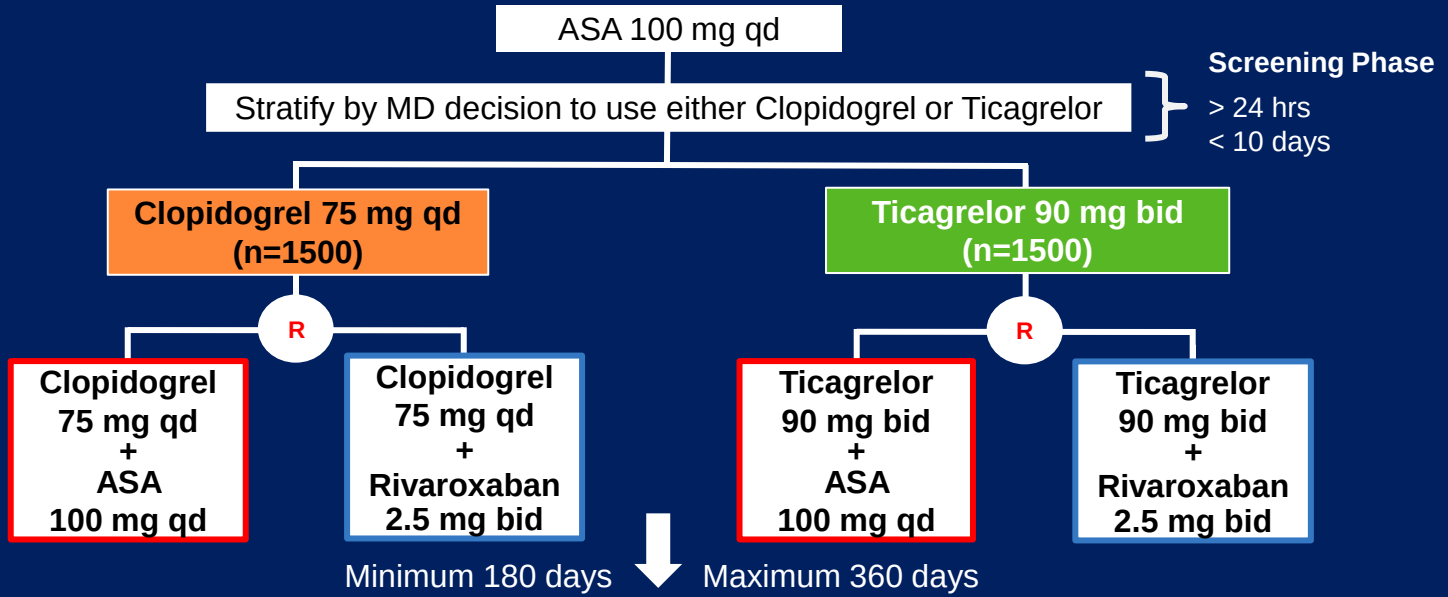
Recent ACS

Stabilized, randomized between 24 hours – 10 days post-event

Exclusions: Bleeding risk, anticoagulant use, prior stroke/TIA

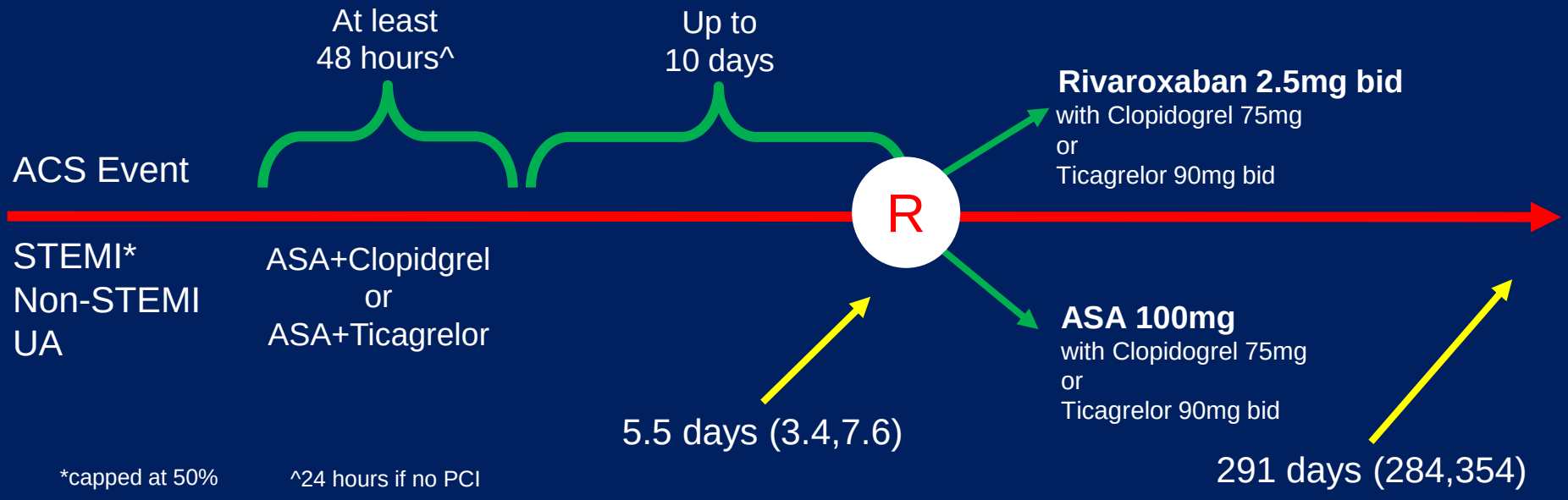


PRIMARY SAFETY ENDPOINT: TIMI non-CABG clinically significant bleeding

EXPLORATORY EFFICACY ENDPOINT: Composite of CV death, MI, ischemic stroke, or stent thrombosis

Protocol Outline

3037 patients; Ticagrelor 1704 patients and Clopidogrel 1333 patients
Adherence to P2Y12 therapy 95% during study period, 6.5% switched P2Y12 therapy



*capped at 50%

^24 hours if no PCI

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Baseline Characteristics: Aspirin vs Rivaroxaban

	Aspirin (N=1518)	Rivaroxaban (N=1519)	Total (N=3037)
Age, median (25th, 75th), yrs	63.0 (57.0, 69.0)	62.0 (57.0, 69.0)	62.0 (57.0, 69.0)
Male sex, no. (%)	1141 (75%)	1134 (75%)	2275 (75%)
White race, no. (%)	1407 (93%)	1417 (93%)	2824 (93%)
Presentation characteristics			
Disease classification, no. (%)			
STEMI	741 (49%)	743 (49%)	1484 (49%)
NSTEMI	612 (40%)	611 (40%)	1223 (40%)
Unstable Angina	165 (11%)	165 (11%)	330 (11%)
Time from hospitalization to randomization, median (25th, 75th), days	5.1 (3.0, 7.3)	5.1 (3.1, 7.2)	5.1 (3.1, 7.2)
Cardiovascular disease history			
Prior MI	345 (23%)	314 (21%)	659 (22%)
Prior PCI	315 (21%)	286 (19%)	601 (20%)
Prior CABG	68 (4%)	58 (4%)	126 (4%)
Prior PAD	74 (5%)	66 (4%)	140 (5%)
Prior heart failure	153 (10%)	157 (10%)	310 (10%)

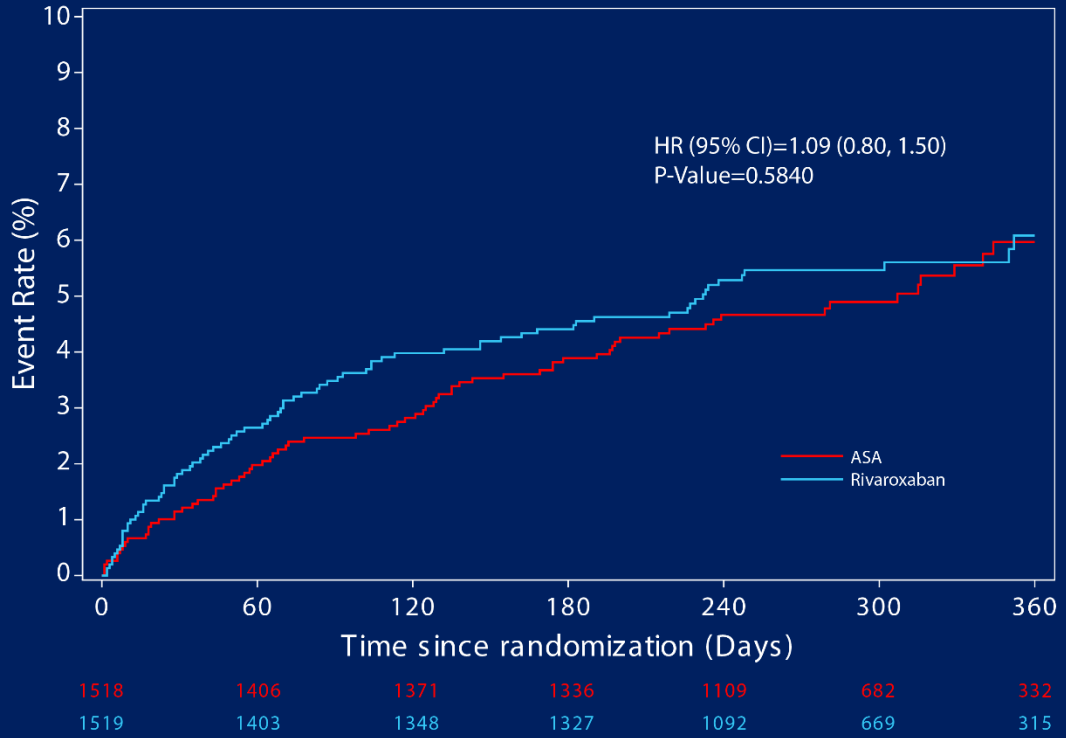
Baseline Characteristics: Aspirin vs Rivaroxaban

	Aspirin (N=1518)	Rivaroxaban (N=1519)	Total (N=3037)
Baseline risk assessment, median (25th, 75th)			
GRACE risk score	97.0 (83.0, 112.0)	96.0 (83.0, 112.0)	96.0 (83.0, 112.0)
Hemoglobin, g/dL	14.1 (13.1, 15.1)	14.2 (13.2, 15.1)	14.1 (13.1, 15.1)
Creatinine clearance, mL/min	87.0 (70.2, 106.2)	87.0 (69.0, 106.8)	87.0 (69.6, 106.8)
Geographic region, no. (%)			
North America	135 (9%)	130 (9%)	265 (9%)
South America	150 (10%)	143 (9%)	293 (10%)
Western Europe	292 (19%)	326 (21%)	618 (20%)
Eastern Europe	373 (25%)	374 (25%)	747 (25%)
Central Europe	488 (32%)	478 (31%)	966 (32%)
Asia & Pacific	80 (5%)	68 (4%)	148 (5%)

Baseline Characteristics: Aspirin vs Rivaroxaban

	Aspirin (N=1518)	Rivaroxaban (N=1519)	Total (N=3037)
Cardiac procedures for index event			
Catheterization performed	1430 (94%)	1425 (94%)	2855 (94%)
PCI performed	1320 (87%)	1325 (87%)	2645 (87%)
Stent placed	1286 (84.7%)	1295 (85.3%)	2581 (85.0%)
DES	870 (68.0%)	859 (66.5%)	1729 (67.3%)
BMS	423 (33.1%)	438 (33.9%)	861 (33.5%)
Bioabsorbable stent	8 (0.6%)	16 (1.2%)	24 (0.9%)
CABG performed	4 (<0.5%)	5 (<0.5%)	9 (<0.5%)
Concomitant medication at randomization, no. (%)			
Beta-blocker	984 (65%)	970 (64%)	1954 (64%)
ACE inhibitors/ARB	960 (63%)	947 (62%)	1907 (63%)
Statins	1065 (70%)	1038 (68%)	2103 (69%)

TIMI Non-CABG Clinically Significant Bleeding



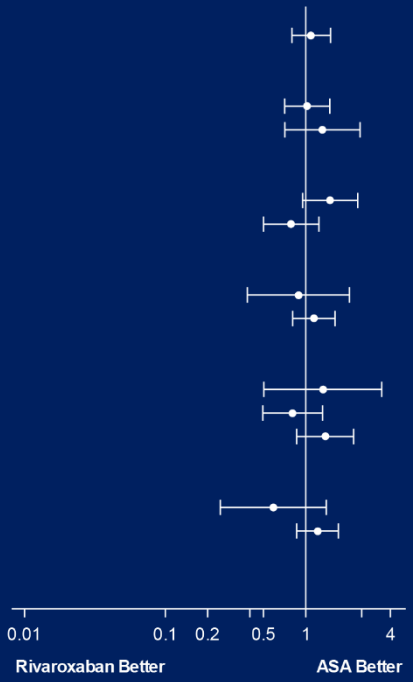
Bleeding Endpoints

	Aspirin (N=1518)	Rivaroxaban (N=1519)	HR (95% CI)	P Value
TIMI Bleeding Categories				
TIMI non-CABG clinically significant bleeding	74 (4.9%)	80 (5.3%)	1.09 (0.80–1.50)	0.5840
TIMI major bleeding†	8 (0.5%)	10 (0.7%)	1.25 (0.49–3.17)	0.6341
TIMI minor bleeding	4 (0.3%)	9 (0.6%)	2.25 (0.69–7.29)	0.1664
GUSTO Bleeding Categories				
GUSTO life threatening or severe bleeding	2 (0.1%)	3 (0.2%)	1.50 (0.25–8.95)	0.6571
GUSTO life threatening, severe, or moderate bleeding	7 (0.5%)	11 (0.7%)	1.58 (0.61–4.08)	0.3395
ISTH Bleeding Categories				
ISTH major bleeding	17 (1.1%)	31 (2.0%)	1.83 (1.01–3.31)	0.0420
BARC Bleeding Categories				
BARC 3a and higher bleeding	13 (0.9%)	22 (1.4%)	1.70 (0.85–3.37)	0.1263

Data presented as no. (%), unless otherwise indicated.
All bleeding events are non-CABG related with the exception of TIMI major. This category includes both non-CABG and CABG related TIMI major bleeding.
†TIMI major bleeding is the only endpoint that includes CABG related bleeding.
BARC indicates Bleeding Academic Research Consortium; CI, confidence interval; GUSTO, Global Use of Strategies to Open Occluded Coronary Arteries; HR, hazard ratio; ISTH, International Society on Thrombosis and Haemostasis; TIMI, Thrombolysis in Myocardial Infarction.

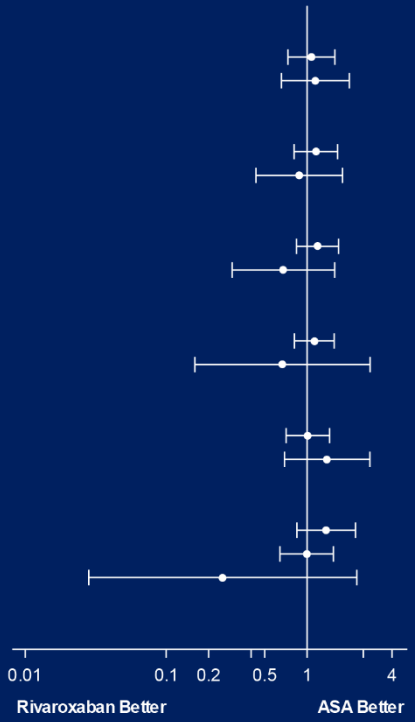
TIMI Non-CABG Clinically Significant Bleeding Subgroups

Characteristic	Number	KM% ASA	KM% Rivaroxaban	Hazard Ratio (95% CI)	Interaction p-value
Overall	3037	5.97	6.08	1.09 (0.80, 1.50)	
Gender					
Male	2275	5.66	5.87	1.02 (0.71, 1.48)	0.4967
Female	762	6.69	6.74	1.31 (0.71, 2.43)	
Age group (years)					
< 65	1776	4.31	5.79	1.49 (0.95, 2.34)	0.0510
≥ 65	1261	8.42	6.56	0.79 (0.50, 1.24)	
Creatinine clearance (ml/min)					
< 60	418	10.54	6.15	0.89 (0.38, 2.04)	0.5817
≥ 60	2474	5.53	6.28	1.14 (0.81, 1.61)	
Index event diagnosis					
Unstable angina	330	4.63	7.41	1.32 (0.50, 3.47)	0.2820
NSTEMI	1223	7.32	5.64	0.81 (0.49, 1.32)	
STEMI	1484	5.14	6.20	1.37 (0.86, 2.18)	
Index PCI					
No	392	10.49	4.80	0.59 (0.25, 1.40)	0.1290
Yes	2645	5.22	6.28	1.21 (0.86, 1.70)	



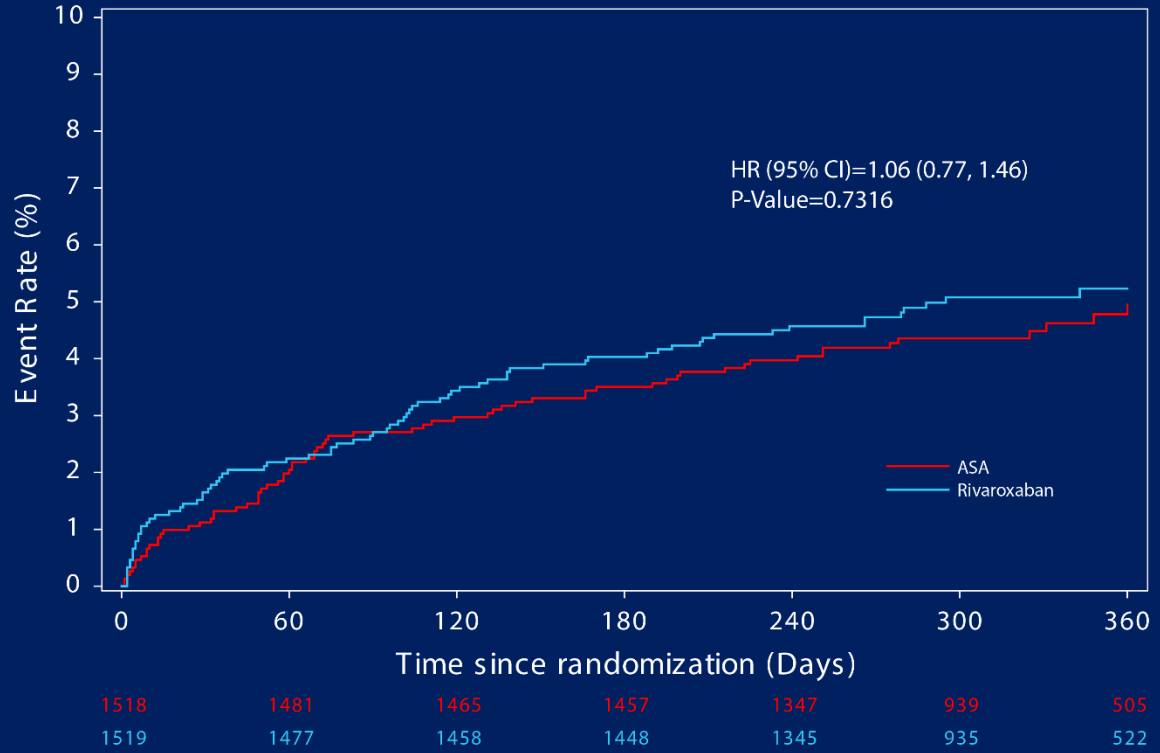
TIMI Non-CABG Clinically Significant Bleeding Subgroups

Characteristic	Number	KM% ASA	KM% Rivaroxaban	Hazard Ratio (95% CI)	Interaction p-value
Diabetes					
No	2131	5.63	5.44	1.07 (0.73, 1.58)	0.8533
Yes	906	6.73	7.66	1.14 (0.66, 1.99)	
Prior MI					
No	2378	5.87	6.45	1.15 (0.81, 1.64)	0.5020
Yes	659	6.31	4.68	0.88 (0.43, 1.78)	
Prior PCI					
No	2436	6.15	6.53	1.18 (0.84, 1.67)	0.2291
Yes	601	5.23	4.17	0.68 (0.29, 1.57)	
Prior CABG					
No	2911	5.86	6.09	1.12 (0.81, 1.55)	0.4879
Yes	126	7.92	5.60	0.67 (0.16, 2.80)	
Current smoking					
No	2040	7.22	6.81	1.01 (0.71, 1.44)	0.4303
Yes	997	3.58	4.52	1.39 (0.69, 2.79)	
GRACE risk score					
<100	1724	3.71	5.16	1.37 (0.85, 2.21)	0.2539
100-140	1197	8.78	7.94	0.99 (0.64, 1.54)	
>140	116	10.70	1.85	0.25 (0.03, 2.25)	



Ischemic Composite Endpoint

CV death, MI, stroke, or definite stent thrombosis



Ischemic Composite Endpoints

	Aspirin (N=1518)	Rivaroxaban (N=1519)	HR (95% CI)	P Value
CV death, MI, stroke, or definite stent thrombosis	72 (4.7%)	76 (5.0%)	1.06 (0.77–1.46)	0.7316
All-cause death	23 (1.5%)	22 (1.4%)	0.95 (0.53–1.71)	0.8771
CV death	17 (1.1%)	19 (1.3%)	1.12 (0.58–2.15)	0.7401
MI	49 (3.2%)	56 (3.7%)	1.15 (0.78–1.68)	0.4872
Stroke	12 (0.8%)	7 (0.5%)	0.58 (0.23–1.48)	0.2506
All stent thrombosis	16 (1.1%)	17 (1.1%)	1.06 (0.54–2.11)	0.8583
Definite stent thrombosis	8 (0.5%)	11 (0.7%)	1.37 (0.55–3.42)	0.4917

Data presented as no. (%), unless otherwise indicated.
CI indicates confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction.

Clopidogrel and Ticagrelor Strata

- Baseline characteristics varied significantly with the choice of P2Y12 inhibitor
  - More Non-STEMI, more cath, PCI, and use in Europe and North America for patients treated with ticagrelor
- The choice of P2Y12 inhibitor was analyzed as a subgroup
  - No significant treatment interaction and P2Y12 inhibitor use for primary bleeding endpoint (p=0.5889) or ischemic endpoints (p=0.3889)
- A limited post-hoc multivariate model for the primary bleeding endpoint noted a higher association with bleeding and ticagrelor use (p=0.0006), but was also associated with region (p=0.02)

Limitations

- This is a phase-2 trial and therefore the results are hypotheses generating
- The patients randomized were on stable DAPT at the time of randomization on average 5 days after their ACS event
- The study population is relative homogenous and treated with high rates of cardiac catheterization and PCI
- Prasugrel was not studied in the trial as this P2Y12 inhibitor is not approved across the full spectrum of ACS

Conclusion

- In this phase-2 trial we observed similar risk of TIMI non-CABG clinically significant bleeding with the combination of rivaroxaban and a P2Y12 inhibitor compared with DAPT
- The ischemic composite outcomes were also similar, but the trial was not powered for assessing this endpoint
- There was no treatment interaction between the choice of P2Y12 inhibitor and randomized treatment of rivaroxaban or ASA on either the primary bleeding or the exploratory ischemic endpoint
- Defining the best intensity of antithrombotic therapy while patients transition from the acute thrombotic setting to chronic prevention deserves more research