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Ticagrelor vs Aspirin in Patients undergoing Coronary-Artery Bypass Grafting

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on behalf of
the TiCAB Investigators

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Deutsches Herzzentrum München
des Freistaates Bayern
Klinik a. d. Technischen Universität München

SCIENTIFIC 2018 SESSIONS

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Unmet Needs After CABG Surgery

- Graft failure is related to major adverse events
- Graft failure peaks in first year post surgery
- More intense platelet inhibition has been shown to prevent graft failure

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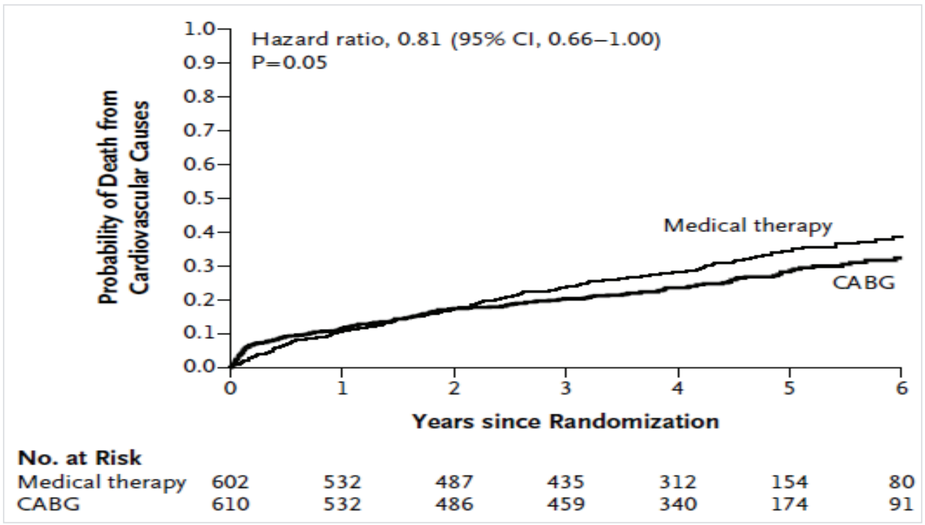
Study Hypothesis

Ticagrelor, as compared to aspirin,

reduces major adverse cardiovascular events

within one year after CABG operation.

TiCAB: Power calculation



STICH trial (CHF):
Mortality 12% at 1 year — N Engl J Med 2009

SYNTAX trial (3VD and LM):
MACCE rate 12.4% at 1 year — N Engl J Med 2009

PLATO-CABG (ACS): MACCE
Ticagrelor/ Aspirin 10.6%
Clopidogrel/ Aspirin: 13.1% — JACC 2011

TiCAB (3VG, LM, 2VD+EF<50% - stable CAD and ACS)

Primary end point: CV death, MI, stroke and revascularisation

- estimated event rate: 13% in the control group
- Two-sided α level of 0.0492 (0.05 adjusted for a planned interim analysis)
- Power of 0.80
- Expected relative risk of 0.775 in the active group
- Total of 3760 patients required

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Secondary Endpoints @ 12 months

- Safety endpoint: Incidence of major bleeding events

- Components of the primary endpoint:
  - Cardiovascular death
  - Myocardial infarction
  - Stroke
  - Recurrent revascularization

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Study Design

- Randomized
- Double blind
- Parallel group
- International multicenter
- Phase III study

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Inclusion Criteria

1. Patients 18 years of age or older – and
2. Informed, written consent by the patient – and
3. Indication for CABG surgery – and
   - coronary three vessel disease, or
   - left main stenosis, or
   - two vessel disease with impaired EF (< 50%)

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Exclusion Criteria

1. Cardiogenic shock, haemodynamic instability
2. Indication for oral anticoagulation or dual antiplatelet therapy
3. Need for concomitant non-coronary surgery (e.g. valve replacement)
4. Contraindication for Aspirin or Ticagrelor use (e.g. known allergy)
5. ....

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Follow-up

- 1st Visit: CABG - Hospital visit
- 2nd Visit: 3 months after CABG - Hospital visit
- 3rd Visit: 6 months after CABG - Telephone visit
- 4th Visit: 9 months after CABG - Telephone visit
- 5th Visit: 12 months after CABG - Hospital visit

TiCAB Trial - Recruitment

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Recruitment (cumulative)
04/2013 – 03/2017

Total recruitment:
1893 patients

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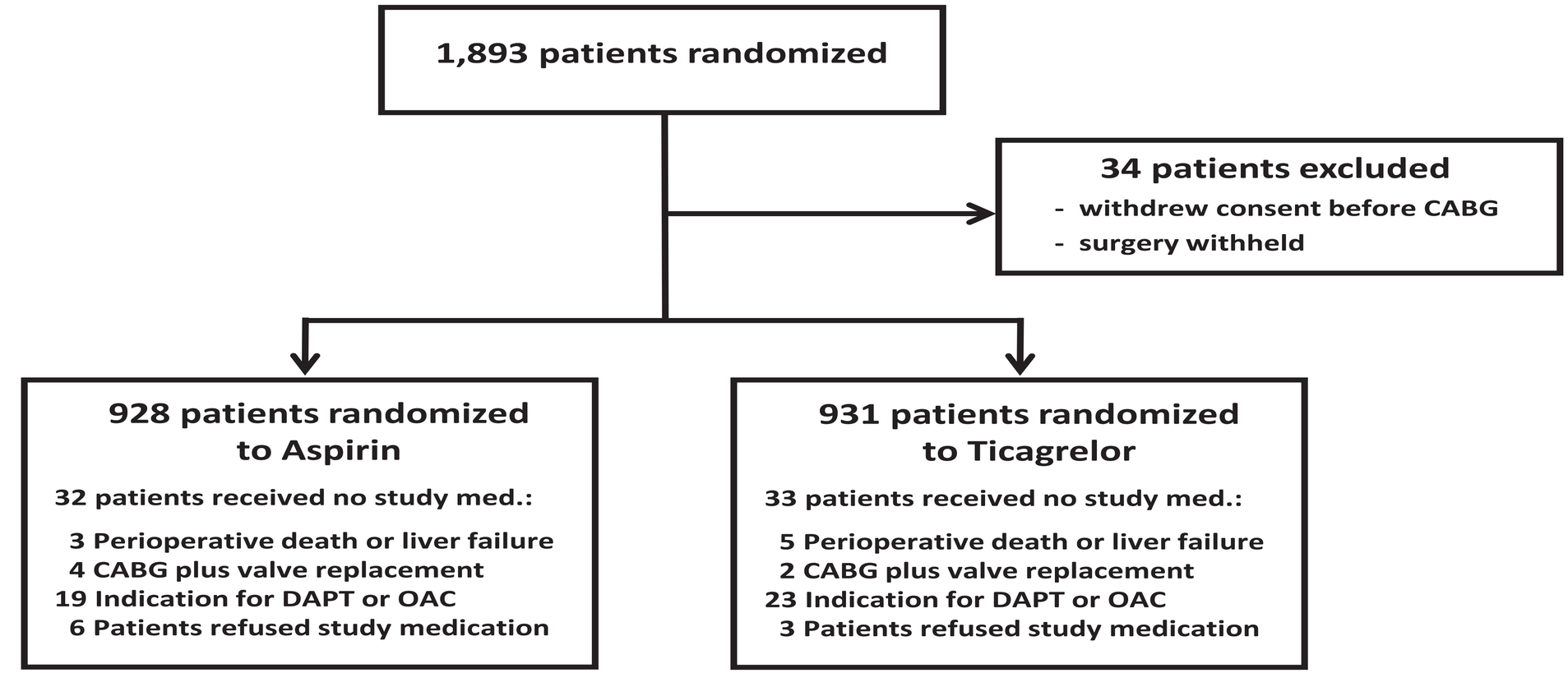
Follow-up

- The trial was continued with in-house funding of the German Heart Center
- The planned interim analysis by the DSMB was scheduled for March 2018
- The DSMB suggested the trial to be stopped

Trial Enrollment, Randomization and Follow-up



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Baseline Characteristics (I)

Characteristics	Aspirin Group (n=928)	Ticagrelor Gr. (n=931)
Male sex, no. (%)	785 (84.6)	794 (85.3)
Age – years	67.0 ± 10.2	66.4 ± 10.1
Stable angina, no. (%)	646 (69.6)	642 (69.0)
Unstable angina, no. (%)	117 (12.6)	126 (13.5)
Non-ST-elevation myocardial infarction, no. (%)	165 (17.8)	163 (17.5)
History of myocardial infarction, no. (%)	204 (22.0)	218 (23.4)
Cardiovascular risk factors		
Hypertension, no. (%)	836 (90.1)	836 (89.8)
Hyperlipidemia, no. (%)	754 (81.3)	765 (82.2)
Smoking, no. (%)	187 (20.2)	200 (21.5)
Ex-Smoking, no. (%)	321 (34.6)	320 (34.4)
Diabetes, no. (%)	330 (35.6)	338 (36.3)
Left ventricular ejection fraction	56.4 ± 12.4	56.6 ± 12.2
< 30 %, no. (%)	16 (1.8)	17 (1.9)
30%-50%, no. (%)	232 (25.6)	225 (24.7)
>50%, no. (%)	646 (71.1)	659 (72.4)

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Baseline Characteristics (II)

Characteristics	Aspirin Group (n=928)	Ticagrelor Gr. (n=931)
Extent of coronary artery disease		
Three vessel disease, no. (%)	858 (92.5)	855 (91.8)
Two vessel disease and EF (< 50 %), no. (%)	60 (6.5)	67 (7.2)
Left main disease, no. (%)	365 (39.3)	387 (41.6)
Medication use		
Aspirin, no. (%)	731 (78.8)	727 (78.1)
P2Y12-Inhibitor, no. (%)	81 (8.7)	98 (10.5)
Ticagrelor, no. (%)	26 (2.8)	37 (4.0)
Prasugrel, no. (%)	0 (0.0)	4 (0.4)
Clopidogrel, no. (%)	55 (5.9)	57 (6.1)
Oral anticoagulant, no. (%)	4 (0.4)	1 (0.1)
β-blockers, no. (%)	606 (65.3)	635 (68.2)
ACEI or ARB, no. (%)	198 (21.3)	242 (26.0)
Calcium antagonist, no. (%)	202 (21.8)	199 (21.4)
Diuretics, no. (%)	288 (31.0)	286 (30.7)
Statins, no. (%)	779 (83.9)	776 (83.4)
Nitrates, no. (%)	53 (5.7)	50 (5.4)
Proton pump inhibitor, no. (%)	264 (28.4)	304 (32.7)

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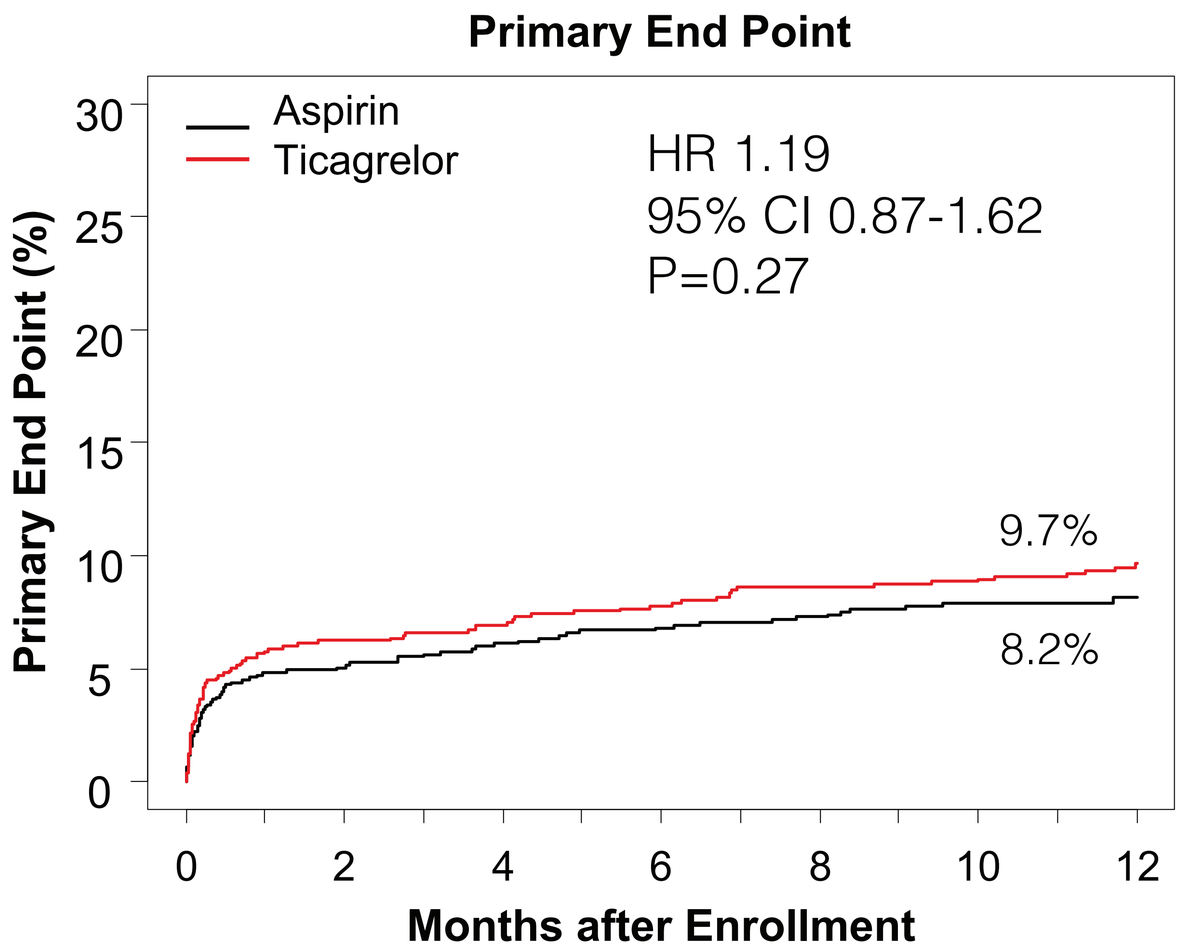
Results – CV death, MI, stroke, repeat revascularization



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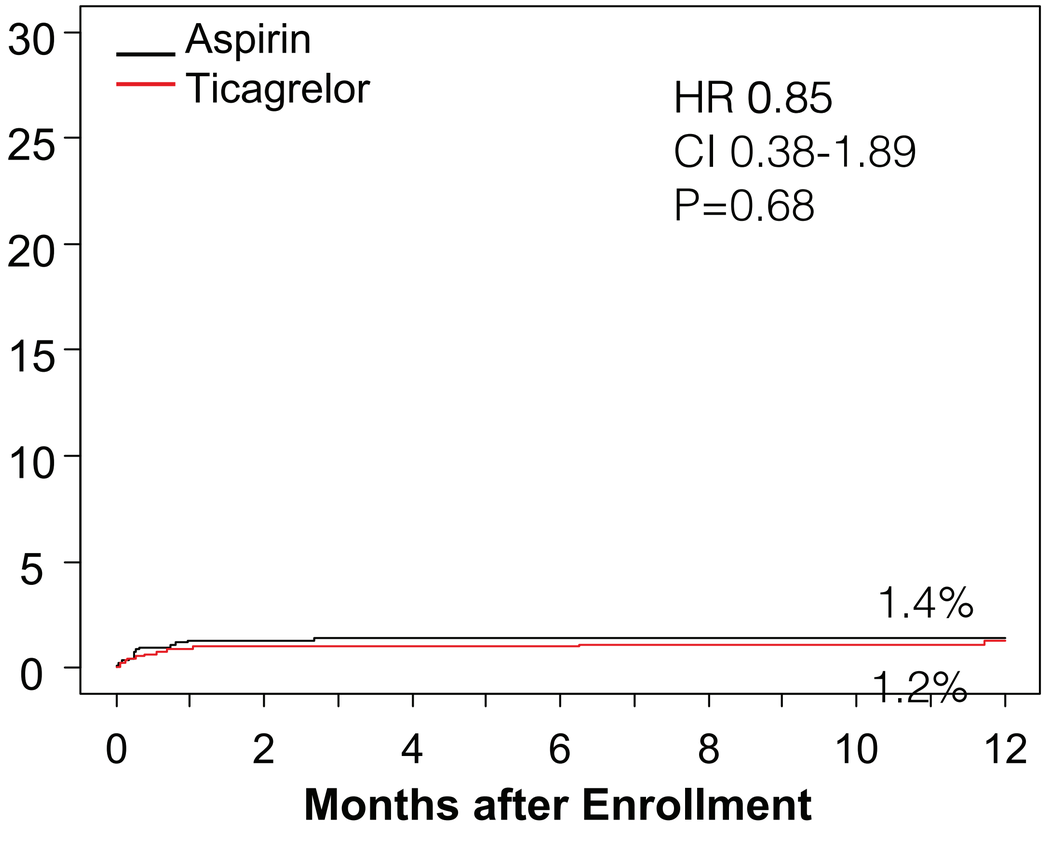
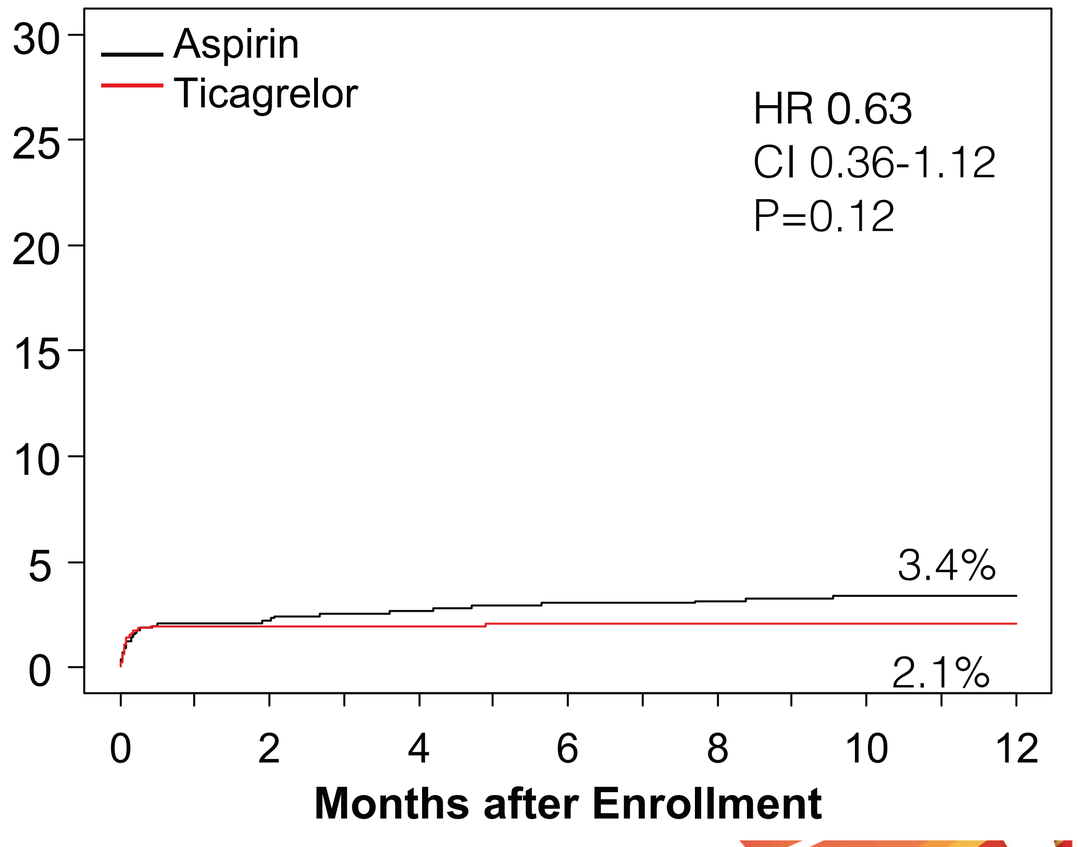
Results – Secondary Endpoints

Cardiovascular Death



Myocardial infarction



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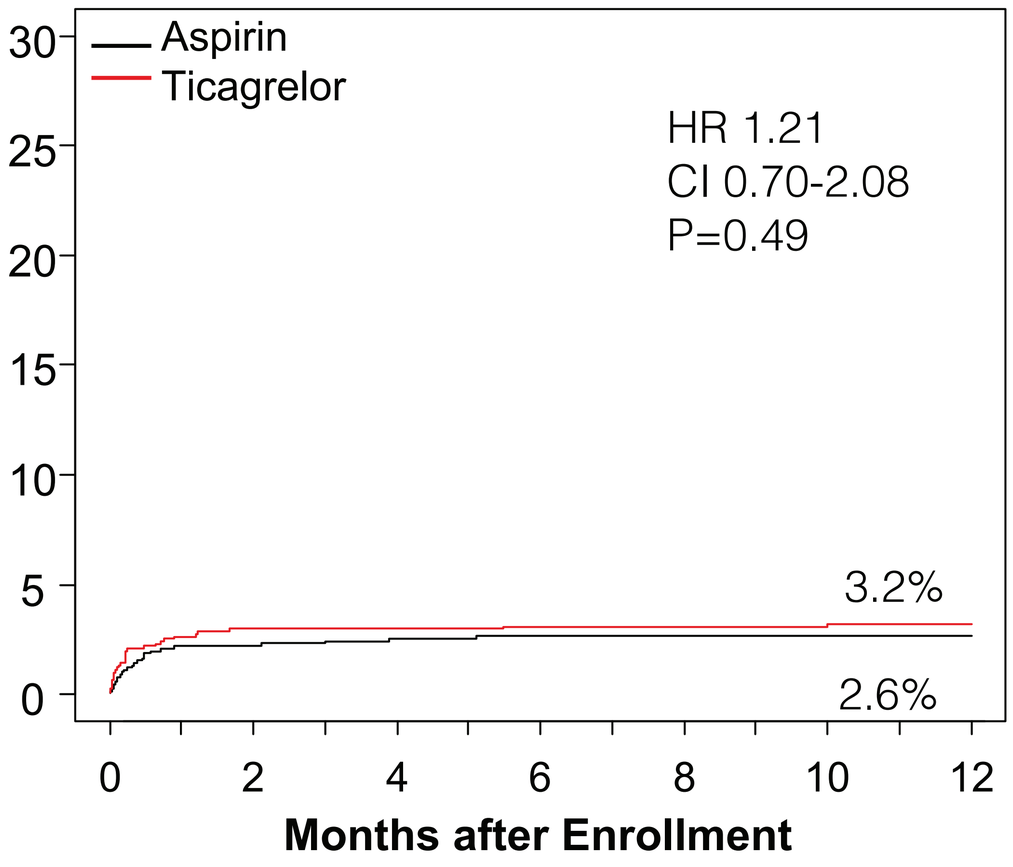
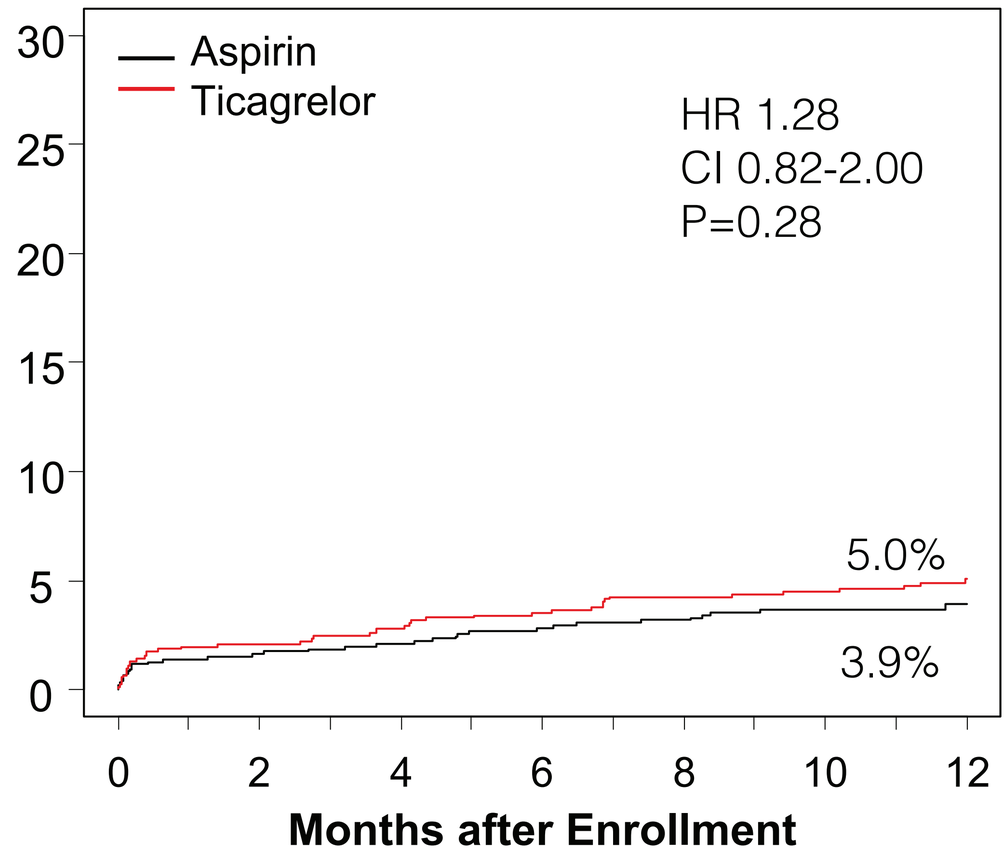
Results – Secondary Endpoints

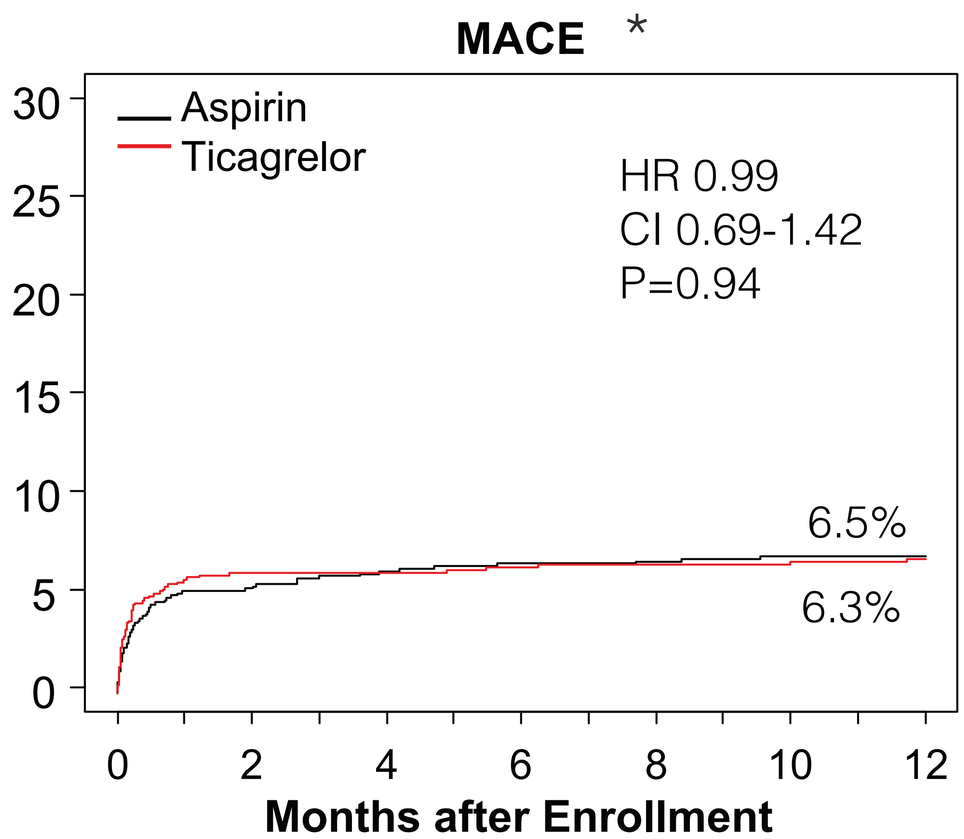
Stroke

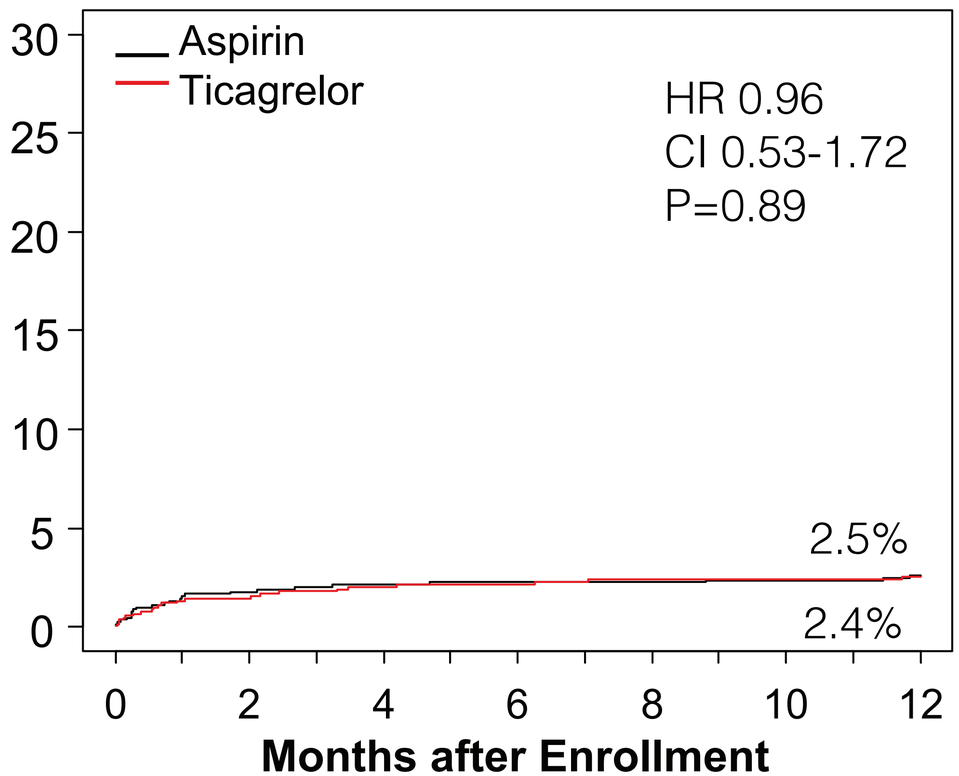


Revascularization



Results – MACE and Total mortality





*CV death, myocardial infarction or stroke

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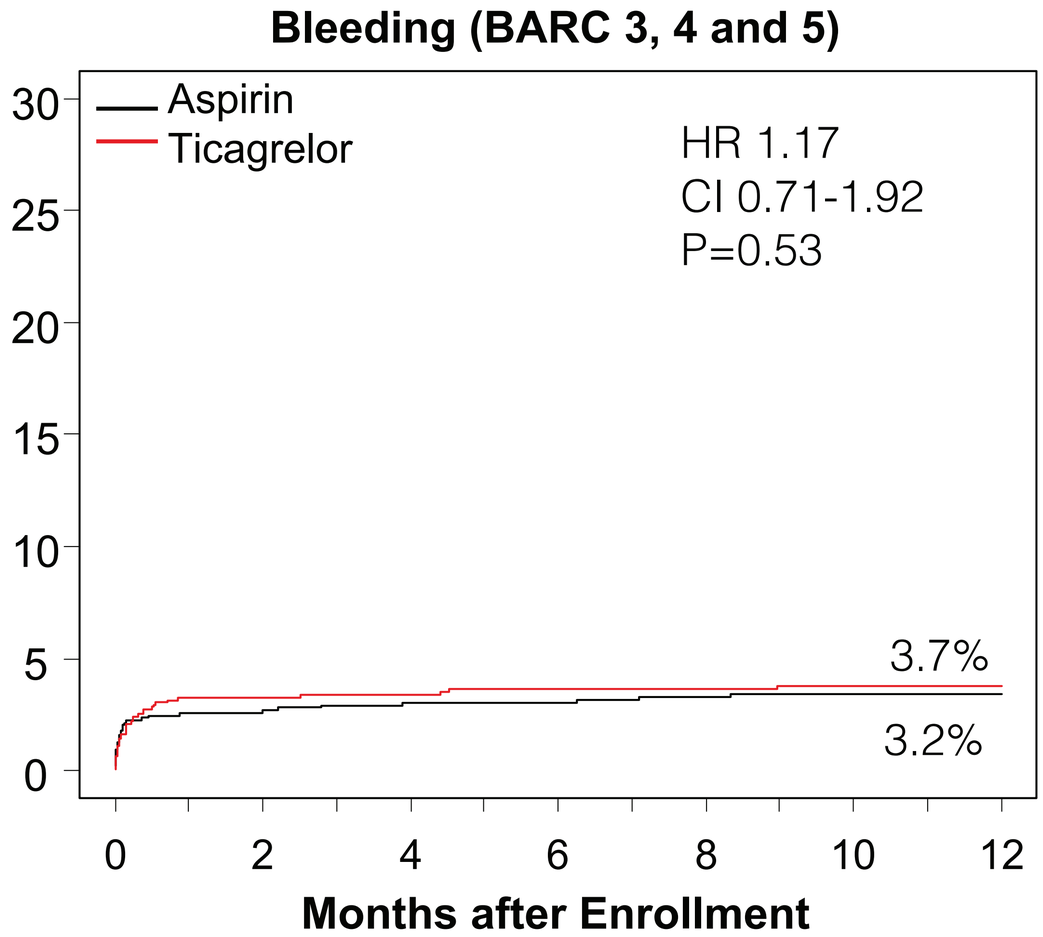
Results – Bleeding events



Aspirin vs Ticagrelor after CABG - TiCAB Trial

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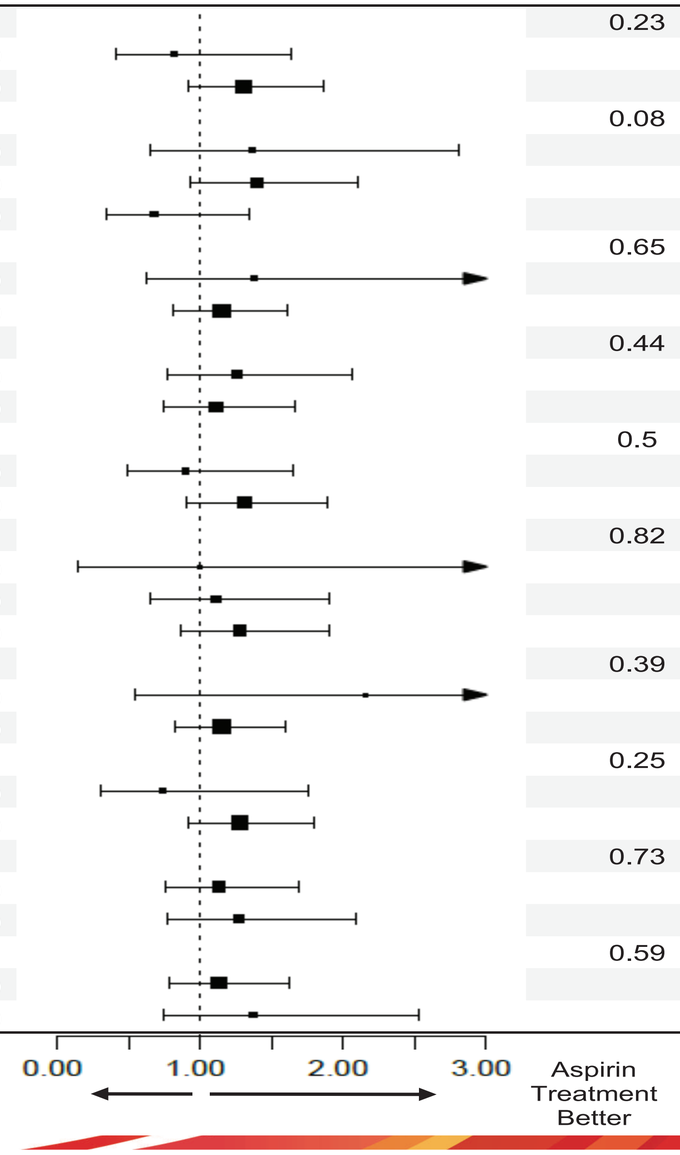
Results – Primary Endpoint Subgroup analysis

Subgroup	Aspirin Group	Ticagrelor Group	Hazard Ratio (95% CI)	p-V Homogeneity
	no. of events (%)			
ACS				0.23
Yes	18/165	15/163	0.82 (0.41-1.63)	
No	55/763	71/768	1.31 (0.92-1.86)	
Age				0.08
>75	14/179	15/148	1.36 (0.66-2.82)	
60-75	39/546	57/575	1.40 (0.93-2.10)	
<60	20/203	14/208	0.68 (0.34-1.34)	
Sex				0.65
Female	11/143	14/137	1.38 (0.63-3.10)	
Male	62/785	72/794	1.15 (0.82-1.62)	
Diabetes				0.44
Yes	28/330	36/338	1.26 (0.77-2.07)	
No	45/593	49/490	1.11 (0.74-1.67)	
PCI				0.5
Yes	22/182	20/193	0.90 (0.49-1.64)	
No	51/744	66/738	1.31 (0.91-1.89)	
LVEF				0.82
<30	2/16	2/17	1.00 (0.14-7.11)	
30-50	26/232	28/225	1.11 (0.65-1.90)	
>50	43/646	55/659	1.28 (0.86-1.90)	
Off-Pump				0.39
Yes	3/32	6/33	2.16 (0.54-8.63)	
No	70/896	80/898	1.15 (0.83-1.59)	
Protocol				0.25
Old	12/122	9/123	0.74 (0.31-1.76)	
New	61/806	77/808	1.28 (0.91-1.79)	
Vein graft				0.73
≥3	44/518	51/536	1.13 (0.76-1.70)	
≤2	29/410	35/395	1.27 (0.78-2.10)	
Arterial graft				0.59
≥1	55/639	62/641	1.13 (0.78-1.62)	
0	18/289	24/290	1.37 (0.74-2.53)	



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Limitations of the Study

- The event rates were lower than expected
- The study was terminated early after half of the anticipated patients were included
- A main source of funding terminated the contract
- Ticagralor displayed no signal for better outcome
- The DSMB suggested to stop recruitment

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Conclusion of the Study

The use of ticagrelor monotherapy instead of aspirin monotherapy in patients undergoing CABG did not significantly impact the rates of major CV events nor major bleeding events.