Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin

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on behalf of the PEGASUS-TIMI 54
Executive & Steering Committees and Investigators

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Background

- Current guidelines recommend adding a $P2Y_{12}$ receptor antagonist to aspirin only for the first year after an acute coronary syndrome (ACS)
- However, several lines of evidence suggest more prolonged therapy may be beneficial in Pts w/ prior MI
  - Landmark analyses from 1-year ACS trials of $P2Y_{12}$ antag
  - Post-hoc MI subgroup analysis from CHARISMA
- Ticagrelor is a potent, reversibly-binding, direct-acting $P2Y_{12}$ antagonist with established efficacy for the first year after an ACS

Hypothesis

The addition of ticagrelor to standard therapy (including low-dose aspirin) would reduce the incidence of major adverse cardiovascular events during long-term follow-up in patients with a history of MI

Trial Organization

TIMI Study Group

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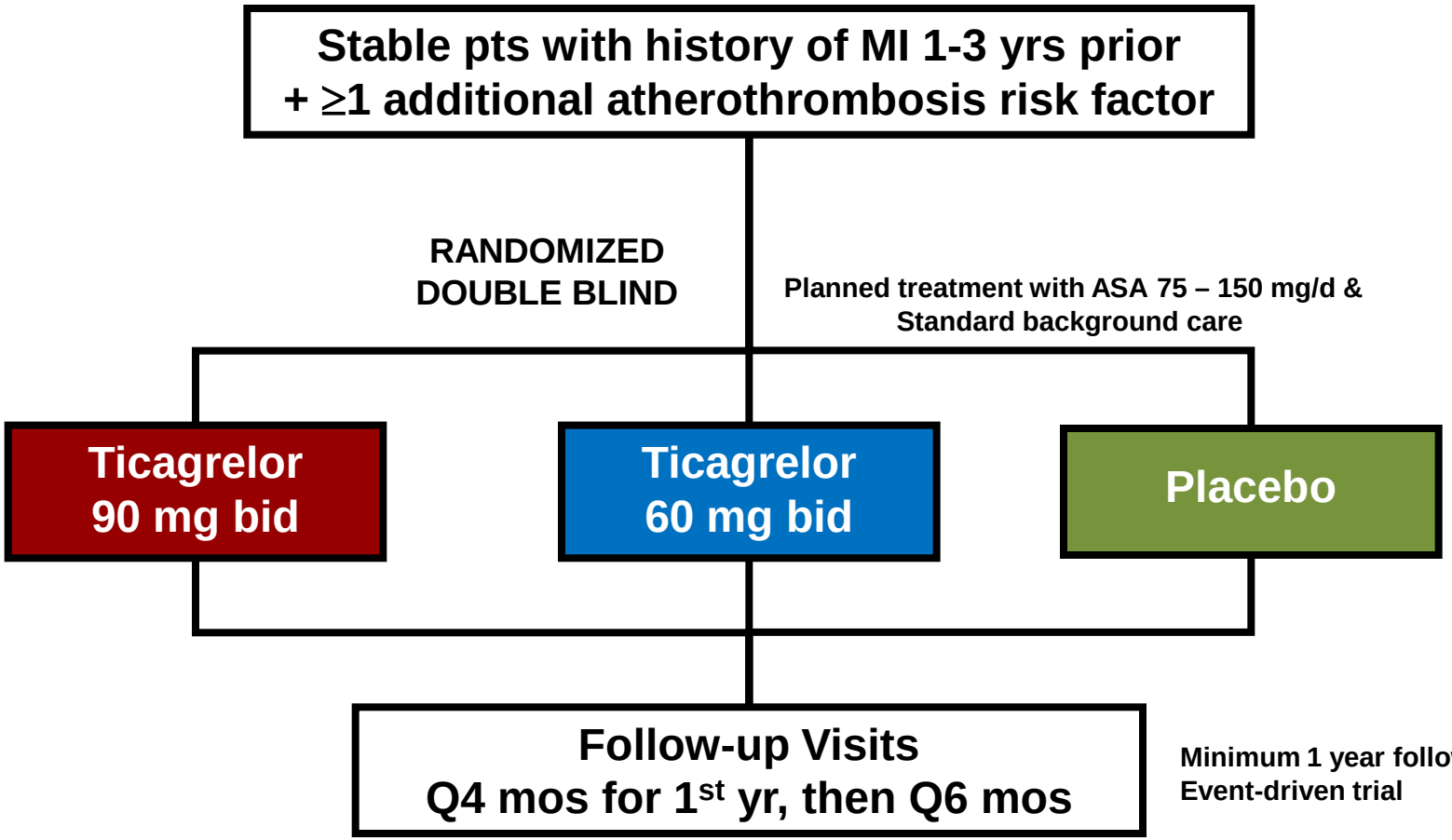
Trial Design



Bonaca MP et al. *Am Heart J* 2014;167:437-44

Key Inclusion & Exclusion Criteria

KEY INCLUSION

- **Age ≥50 years**
- At least 1 of the following:
  - **Age ≥65 years**
  - Diabetes requiring medication
  - 2nd prior MI (>1 year ago)
  - Multivessel CAD
  - CrCl <60 mL/min
- Tolerating ASA and able to be dosed at 75-150 mg/d

KEY EXCLUSION

- Planned use of $P2Y_{12}$ antagonist, dipyridamole, cilostazol, or anticoag
- Bleeding disorder
- History of ischemic stroke, ICH, CNS tumor or vascular abnormality
- Recent GI bleed or major surgery
- At risk for bradycardia
- Dialysis or severe liver disease

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Endpoints

- **Efficacy: hierarchical testing**
  - Primary: cardiovascular (CV) death, MI, or stroke
  - Secondary: CV death; all-cause mortality
  - Prespecified exploratory: substituting coronary for CV death; other individual coronary and cerebrovascular ischemic outcomes; pooling ticagrelor doses
- **Safety**
  - Primary: TIMI Major Bleeding
  - Other: intracranial hemorrhage (ICH), fatal bleeding
  - AEs/SAEs
- **TIMI Clinical Events Committee (CEC)**
  - Adjudicated all efficacy endpoints & bleeding events
  - Members unaware of treatment assignments

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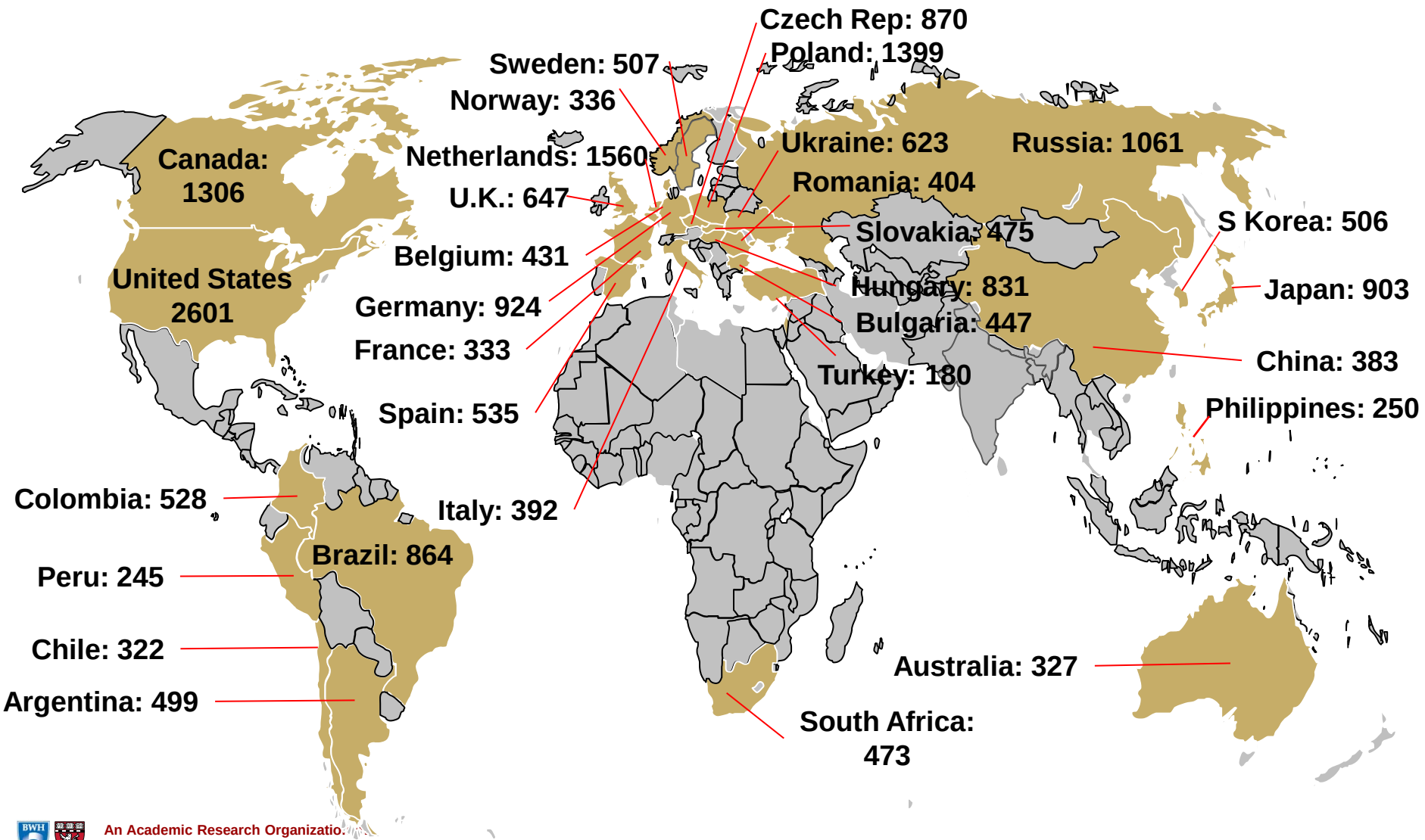
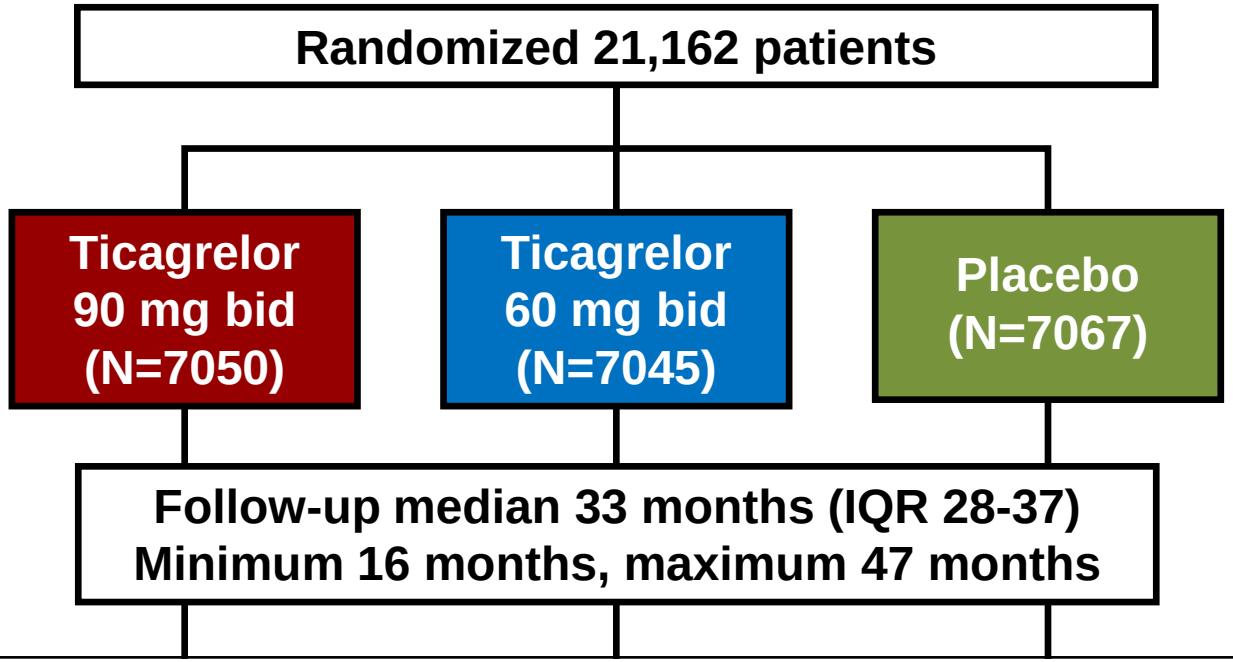
Global Enrollment

21,162 patients randomized at 1161 sites in 31 countries between 10/2010 – 5/2013



Follow-Up



Premature perm. drug discontinuation	**12%/yr**	**11%/yr**	**8%/yr**
Withdrew consent	**0.7% total**	**0.7% total**	**0.7% total**
Lost to follow-up	**3 patients**	**6 patients**	**1 patient**

Ascertainment for primary endpoint was complete for 99% of potential patient-years of follow up

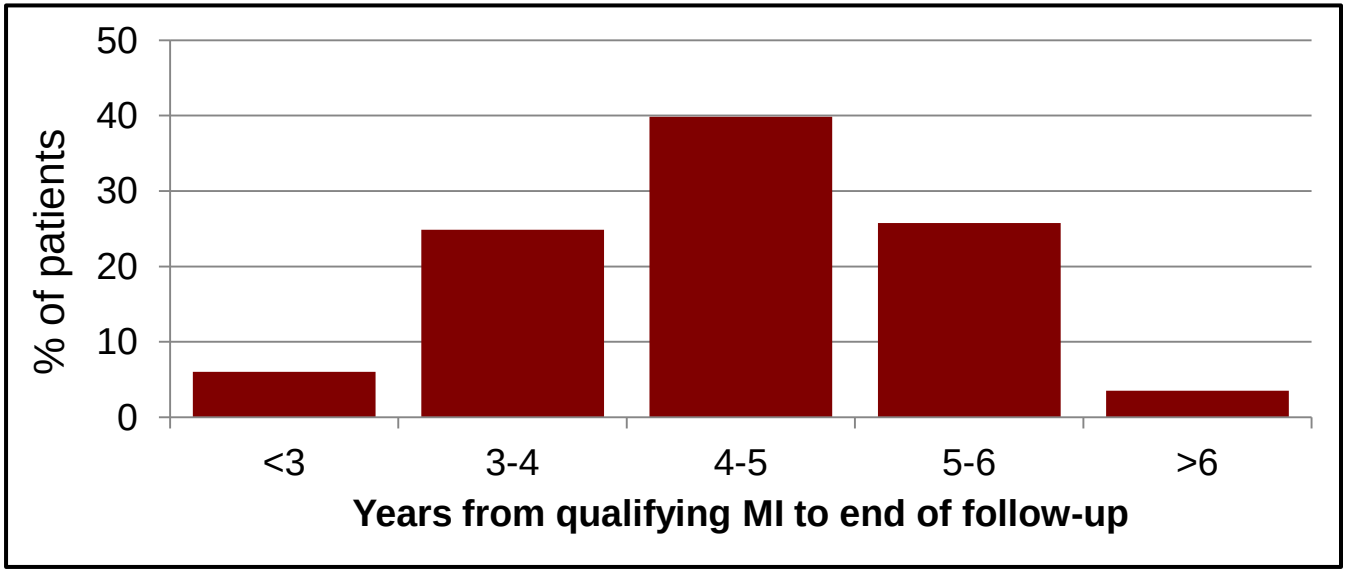
Baseline Characteristics

Characteristic	Value
Age – yr, mean (SD)	65 (8)
Female	24
Hypertension	78
Hypercholesterolemia	77
Current smoker	17
Diabetes mellitus	32
Estimated GFR <60 mL/min/1.73m^2	23
History of PCI	83
Multivessel coronary disease	59
History of more than 1 prior MI	17

No difference between treatment arms.
Values for categorical variables are %.

Baseline Characteristics

Characteristic	Value
Qualifying Event	
Years from MI – median (IQR)	**1.7 (1.2 – 2.3)**
History of STEMI	**53**
History of NSTEMI	**41**
MI type unknown	**6**



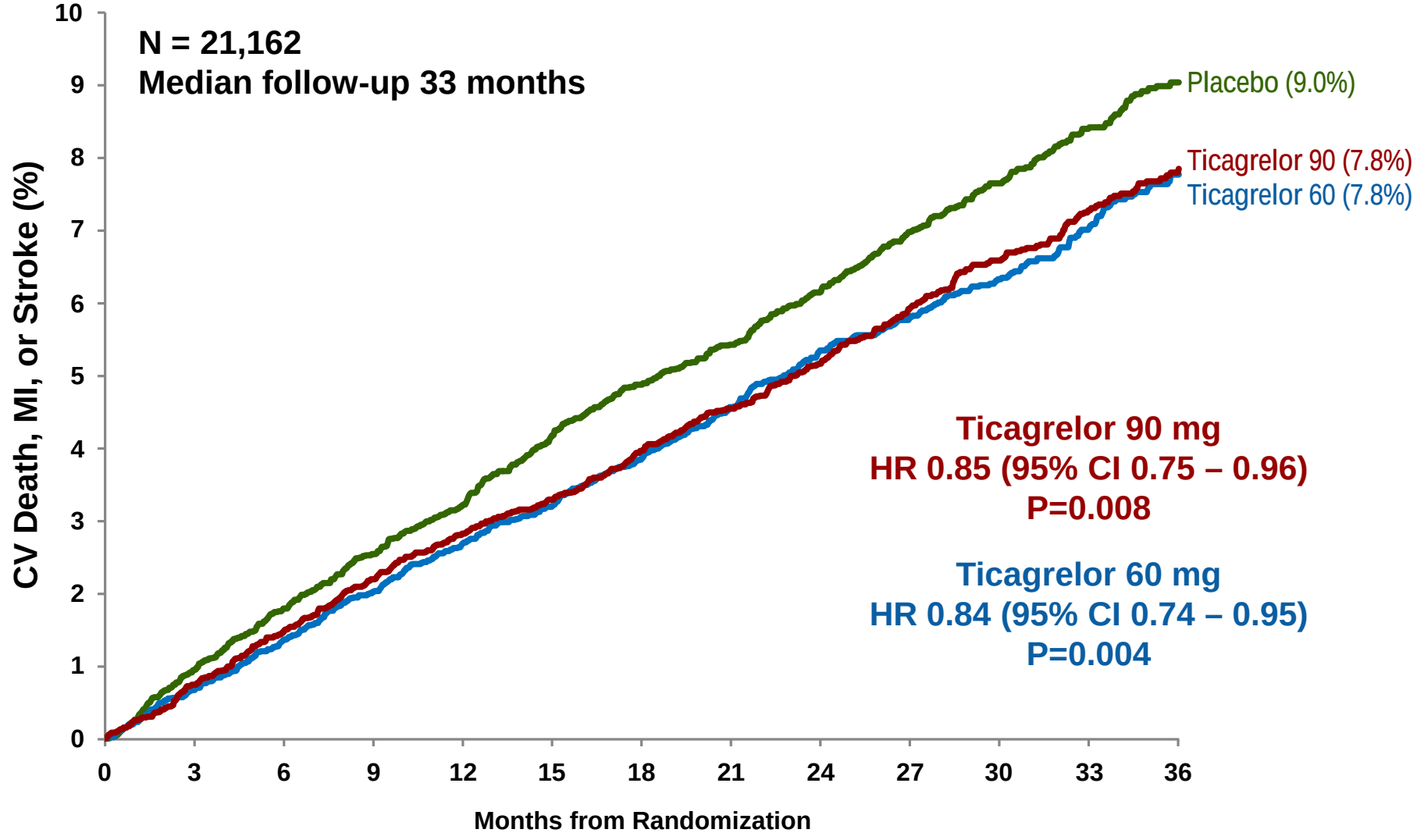
No difference between treatment arms.
Values for categorical variables are %.

Baseline Characteristics

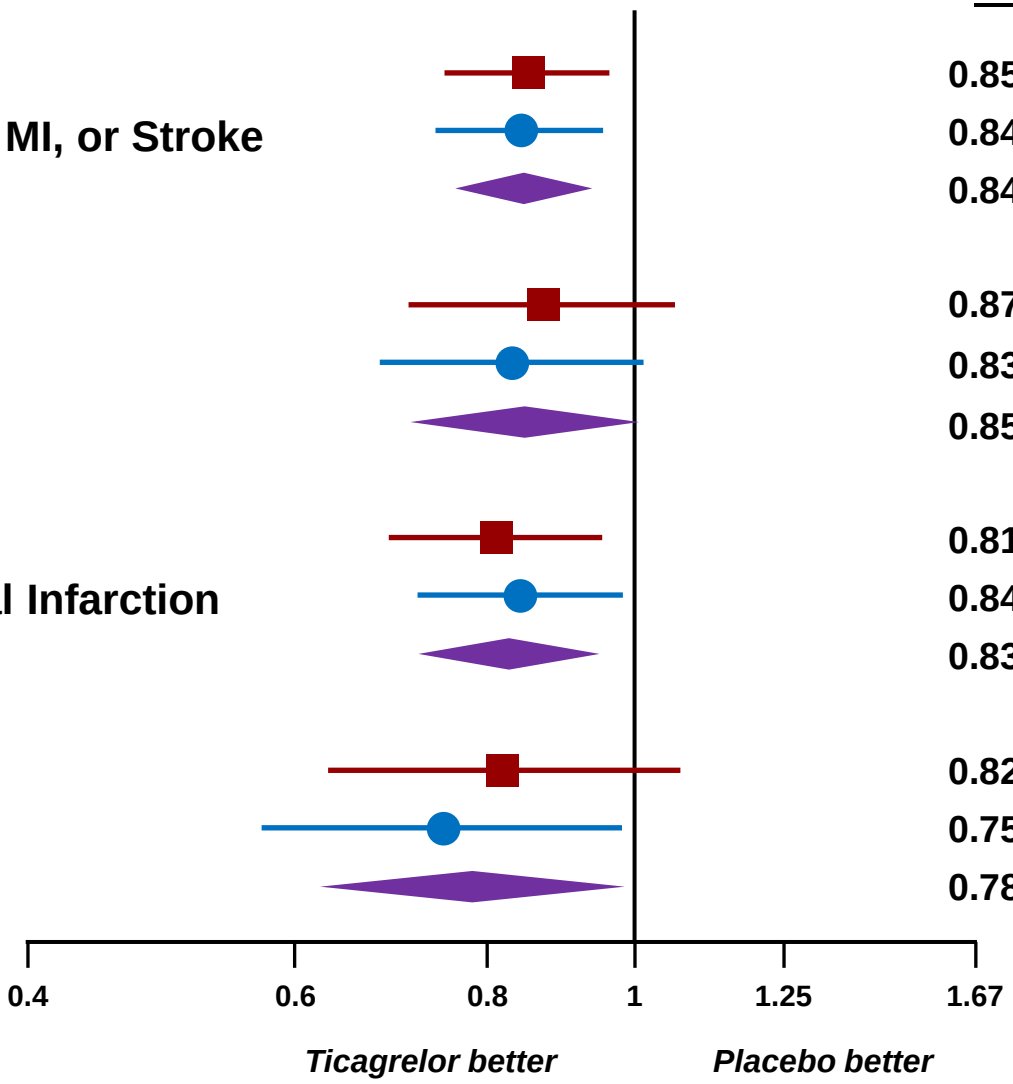
Characteristic	Value
Qualifying Event	
Years from MI – median (IQR)	1.7 (1.2 – 2.3)
History of STEMI	53
History of NSTEMI	41
MI type unknown	6
Medications at enrollment	
Aspirin (any dose)	99.9
Dose 75-100 mg/d	97.3
Statin	93
Beta-blocker	82
ACEI or ARB	80

No difference between treatment arms.
Values for categorical variables are %.

Primary Endpoint



Components of Primary Endpoint



Endpoint	HR (95% CI)	P value
CV Death, MI, or Stroke (1558 events)	0.85 (0.75-0.96)	0.008
	0.84 (0.74-0.95)	0.004
	0.84 (0.76-0.94)	0.001
CV Death (566 events)	0.87 (0.71-1.06)	0.15
	0.83 (0.68-1.01)	0.07
	0.85 (0.71-1.00)	0.06
Myocardial Infarction (898 events)	0.81 (0.69-0.95)	0.01
	0.84 (0.72-0.98)	0.03
	0.83 (0.72-0.95)	0.005
Stroke (313 events)	0.82 (0.63-1.07)	0.14
	0.75 (0.57-0.98)	0.03
	0.78 (0.62-0.98)	0.03

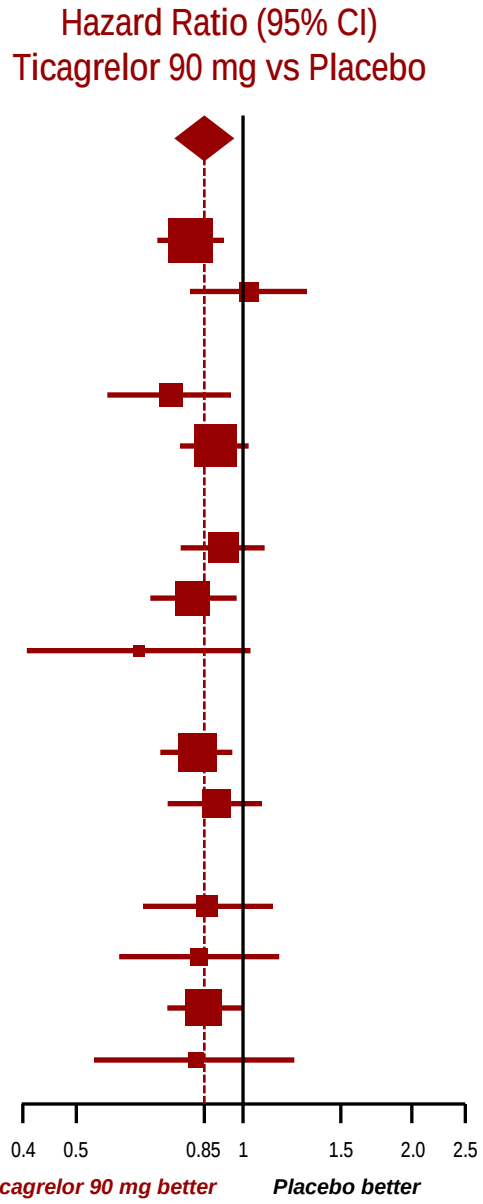
Ticagrelor 90 mg
Ticagrelor 60 mg
Pooled

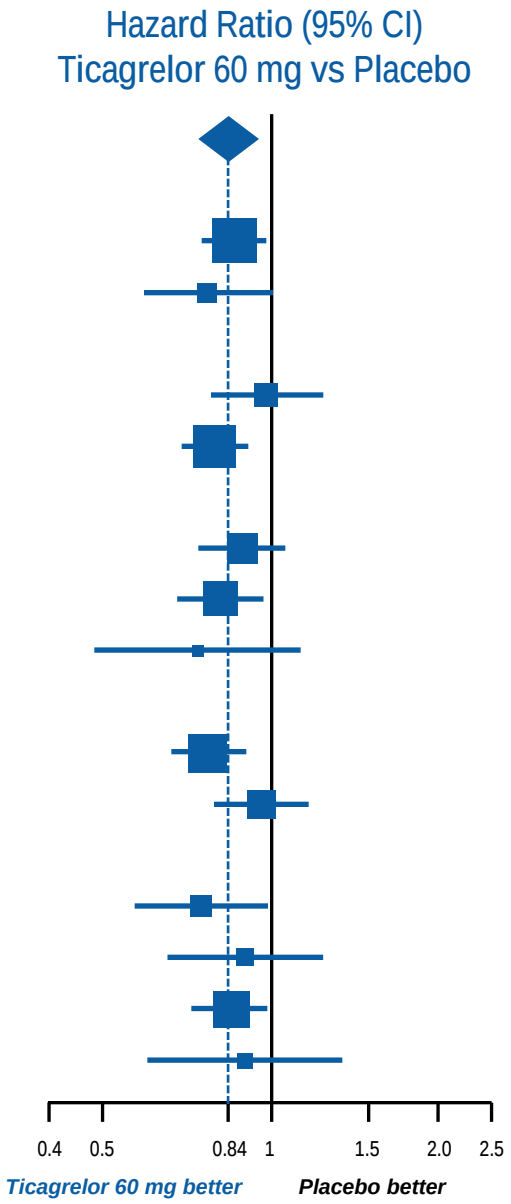
Other Efficacy Outcomes

Outcome	Ticagrelor 90 mg bid (N=7050)	Ticagrelor 60 mg bid (N=7045)	Placebo (N=7067)	Ticagrelor 90 vs Placebo p-value	Ticagrelor 60 vs Placebo p-value
	3-yr KM rate (%)				
Coronary Death, MI, or Stroke	7.0	7.1	8.3	HR 0.82 P=0.002	HR 0.83 P=0.003
Coronary Death or MI	5.6	5.8	6.7	HR 0.81 P=0.004	HR 0.84 P=0.01
Coronary Death	1.5	1.7	2.1	HR 0.73 P=0.02	HR 0.80 P=0.09
Death from any cause	5.2	4.7	5.2	HR 1.00 P=0.99	HR 0.89 P=0.14

Efficacy for 1° EP in Subgroups

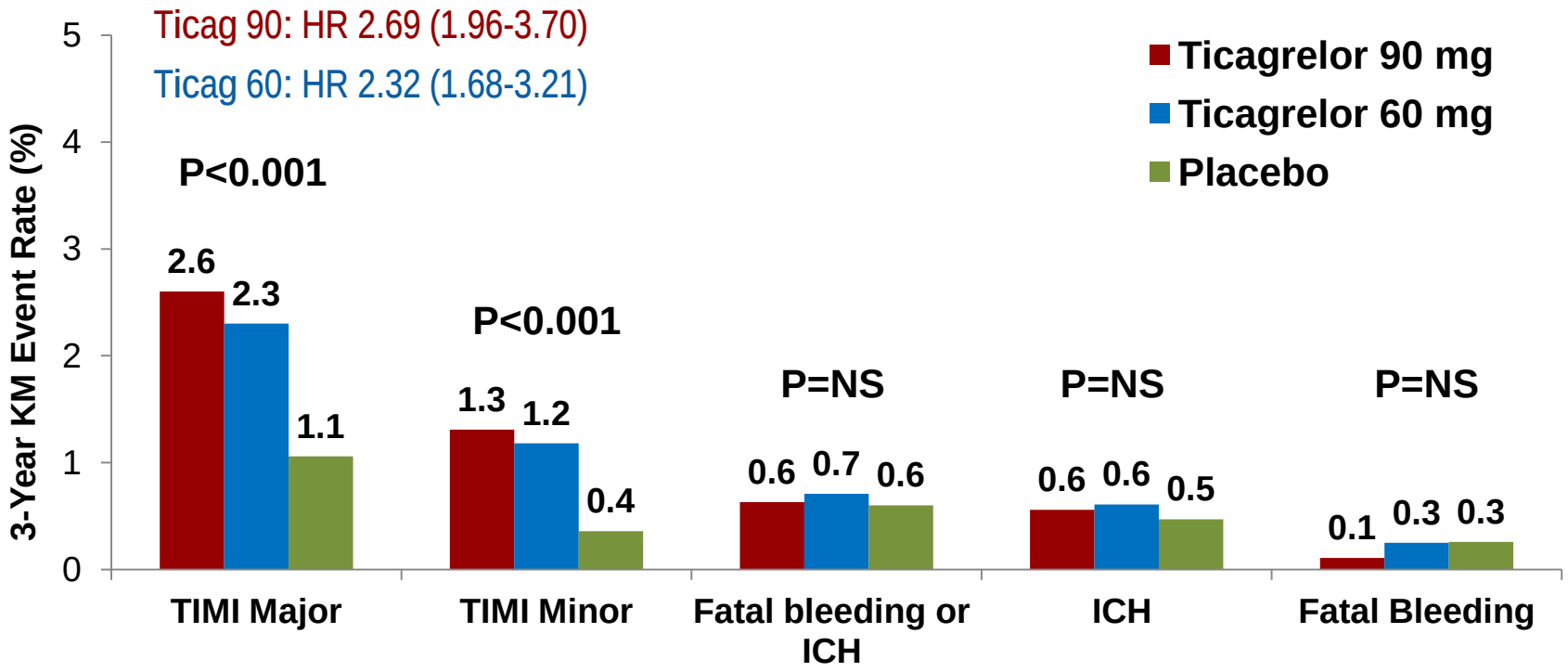
Subgroup	Pts
All Patients	21,162
Age at Randomization	
Age < 75	18,079
Age ≥ 75	3,083
Sex	
Female	5,060
Male	16,102
Qualifying MI	
NSTEMI	8,583
STEMI	11,329
Unknown	1,223
Time from Qualifying MI	
< 2 years	12,980
≥ 2 years	8,155
Region	
North America	3,907
South America	2,458
Europe	12,428
Asia	2,369





All P values for heterogeneity >0.05

Bleeding


Ticag 90: HR 2.69 (1.96-3.70)
Ticag 60: HR 2.32 (1.68-3.21)
Ticagrelor 90 mg
Ticagrelor 60 mg
Placebo
3-Year KM Event Rate (%)
0
1
2
3
4
5
P<0.001
2.6
2.3
1.1
P<0.001
1.3
1.2
0.4
P=NS
0.6
0.7
0.6
P=NS
0.6
0.6
0.5
P=NS
0.1
0.3
0.3
TIMI Major
TIMI Minor
Fatal bleeding or ICH
ICH
Fatal Bleeding

Other Adverse Events

Adverse Event	Ticagrelor 90 mg bid (N=6988)	Ticagrelor 60 mg bid (N=6958)	Placebo (N=6996)	Ticagrelor 90 vs Placebo p-value	Ticagrelor 60 vs Placebo p-value
	3-yr KM rate (%)				
Dyspnea AE	18.9	15.8	6.4	P<0.001	P<0.001
Leading to study drug d/c	6.5	4.6	0.8	P<0.001	P<0.001
Severe	1.2	0.6	0.2	P<0.001	P<0.001
Bradyarrhythmia	2.0	2.3	2.0	P=0.31	P=0.10
Gout	2.3	2.0	1.5	P<0.001	P=0.01

Summary

- Adding ticagrelor to low-dose aspirin in stable patients with a history of MI reduced the risk of CV death, MI or stroke
- The benefit of ticagrelor was consistent
  - For both fatal & non-fatal components of primary endpoint
  - Over the duration of treatment
  - Among major clinical subgroups
- Ticagrelor increased the risk of TIMI major bleeding, but not fatal bleeding or ICH
- The two doses of ticagrelor had similar overall efficacy, but bleeding and other side effects tended to be less frequent with 60 mg bid dose

Conclusion

Long-term dual antiplatelet therapy with low-dose aspirin and ticagrelor should be considered in appropriate patients with a myocardial infarction.