



**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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- **Current guidelines recommend adding a P2Y₁₂ 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 P2Y₁₂ antag
 - Post-hoc MI subgroup analysis from CHARISMA
- **Ticagrelor is a potent, reversibly-binding, direct-acting P2Y₁₂ antagonist with established efficacy for the first year after an ACS**

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

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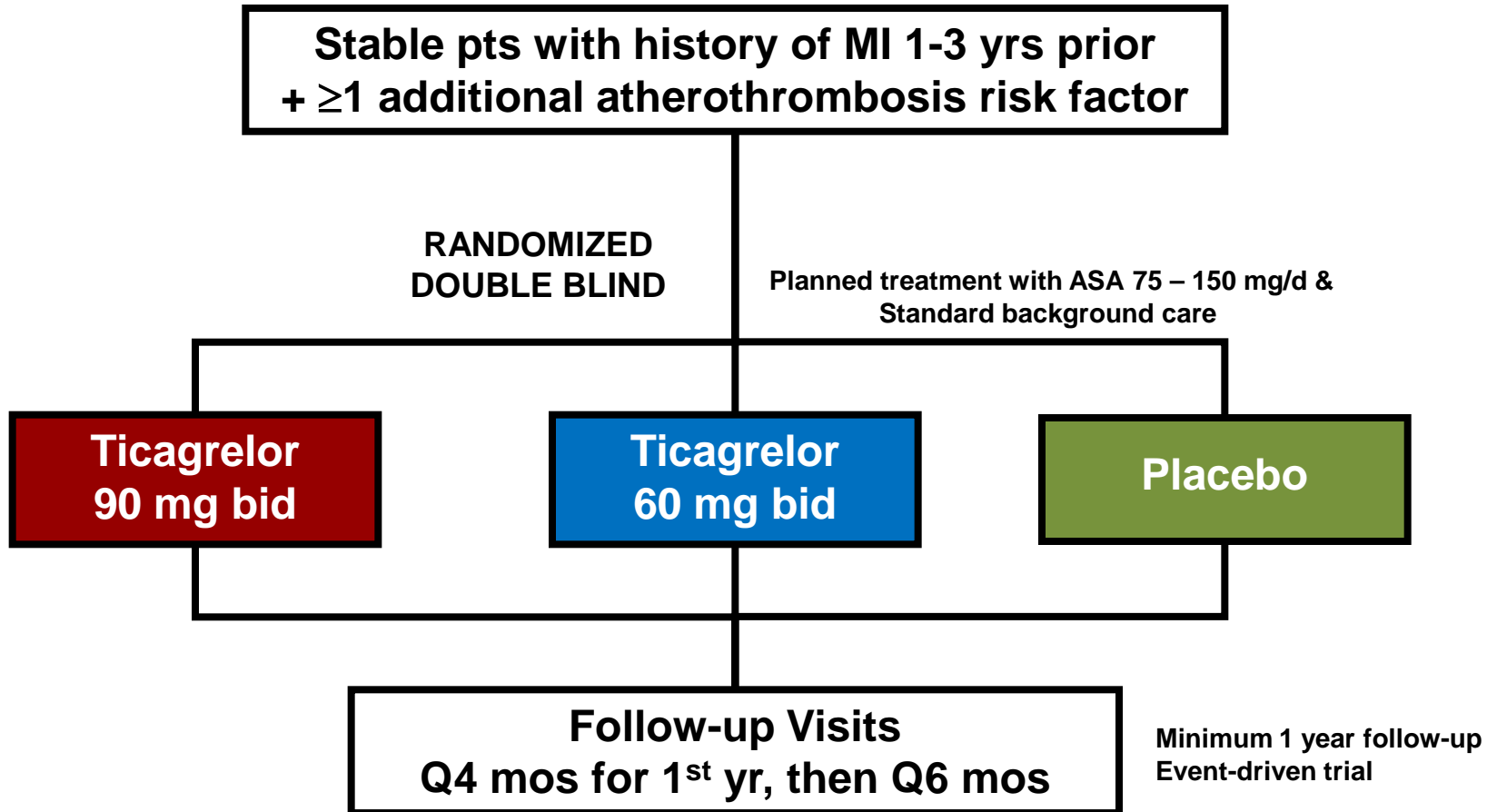
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KEY INCLUSION

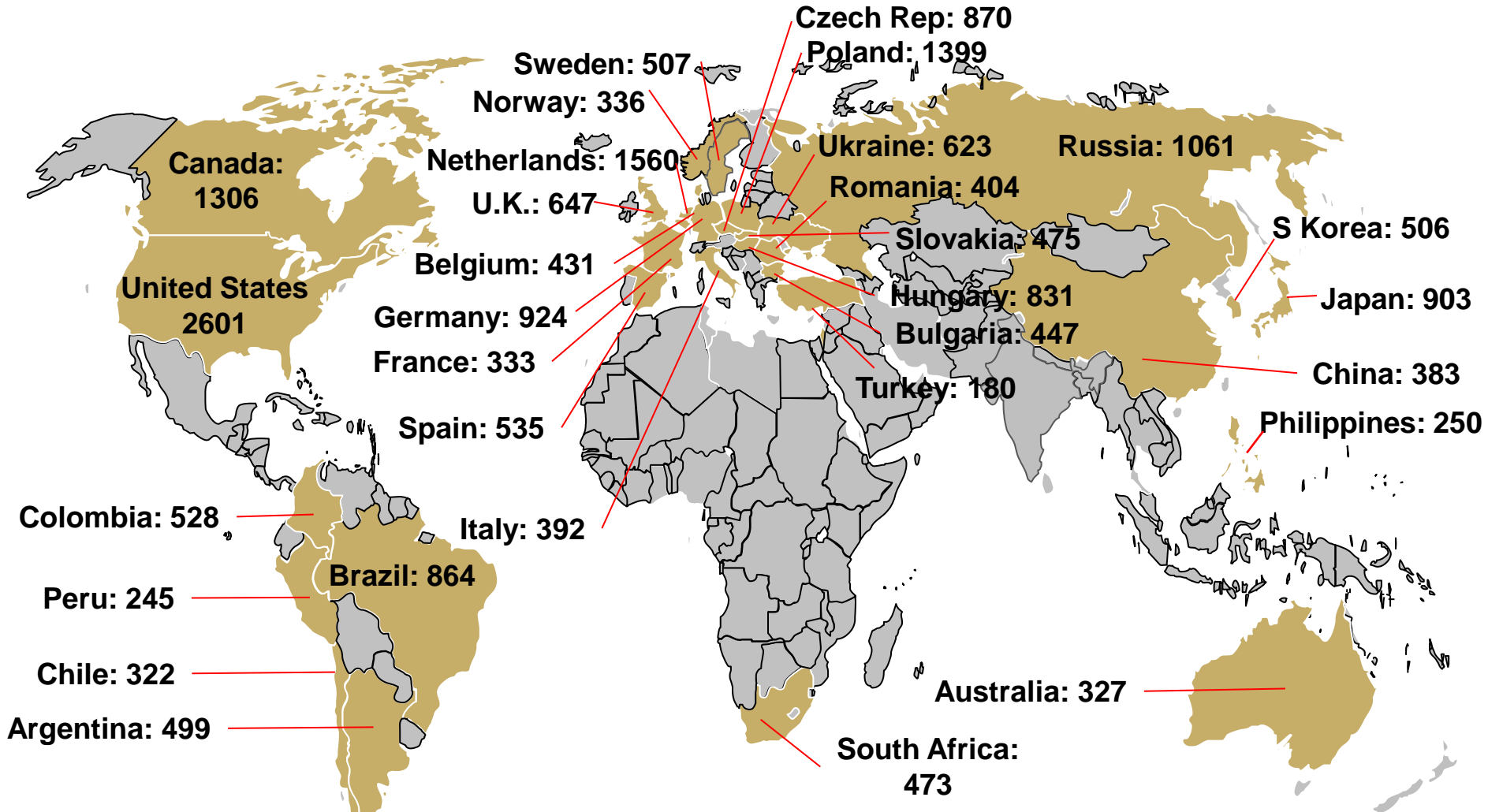
- Age ≥ 50 years
- At least 1 of the following:
 - Age ≥ 65 years
 - Diabetes requiring medication
 - 2nd prior MI (>1 year ago)
 - Multivessel CAD
 - CrCl <60 mL/min
- Tolerating ASA and able to be dosed at 75-150 mg/d

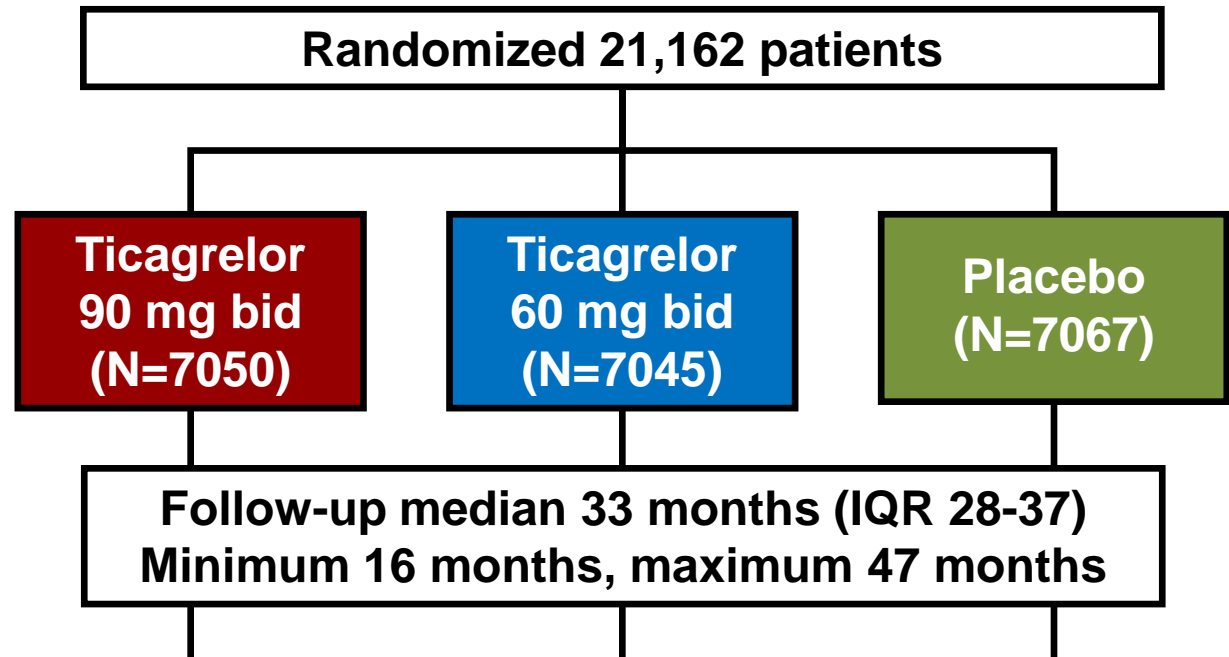
KEY EXCLUSION

- Planned use of P2Y₁₂ 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

- **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

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





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

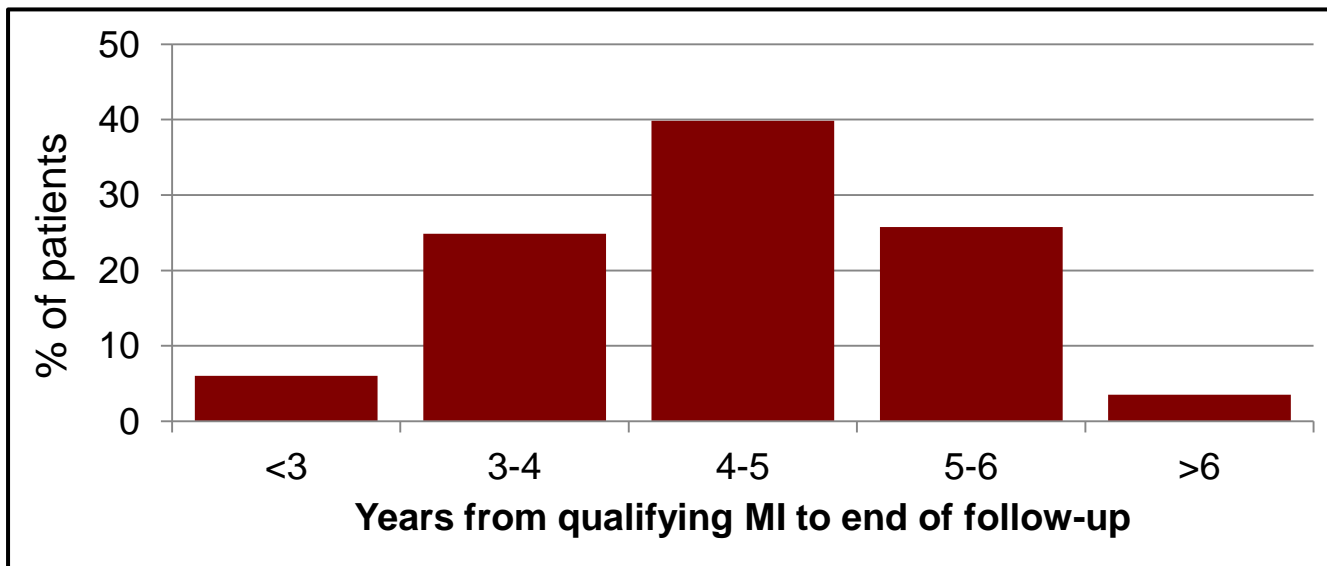
1 patient

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

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 %.

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

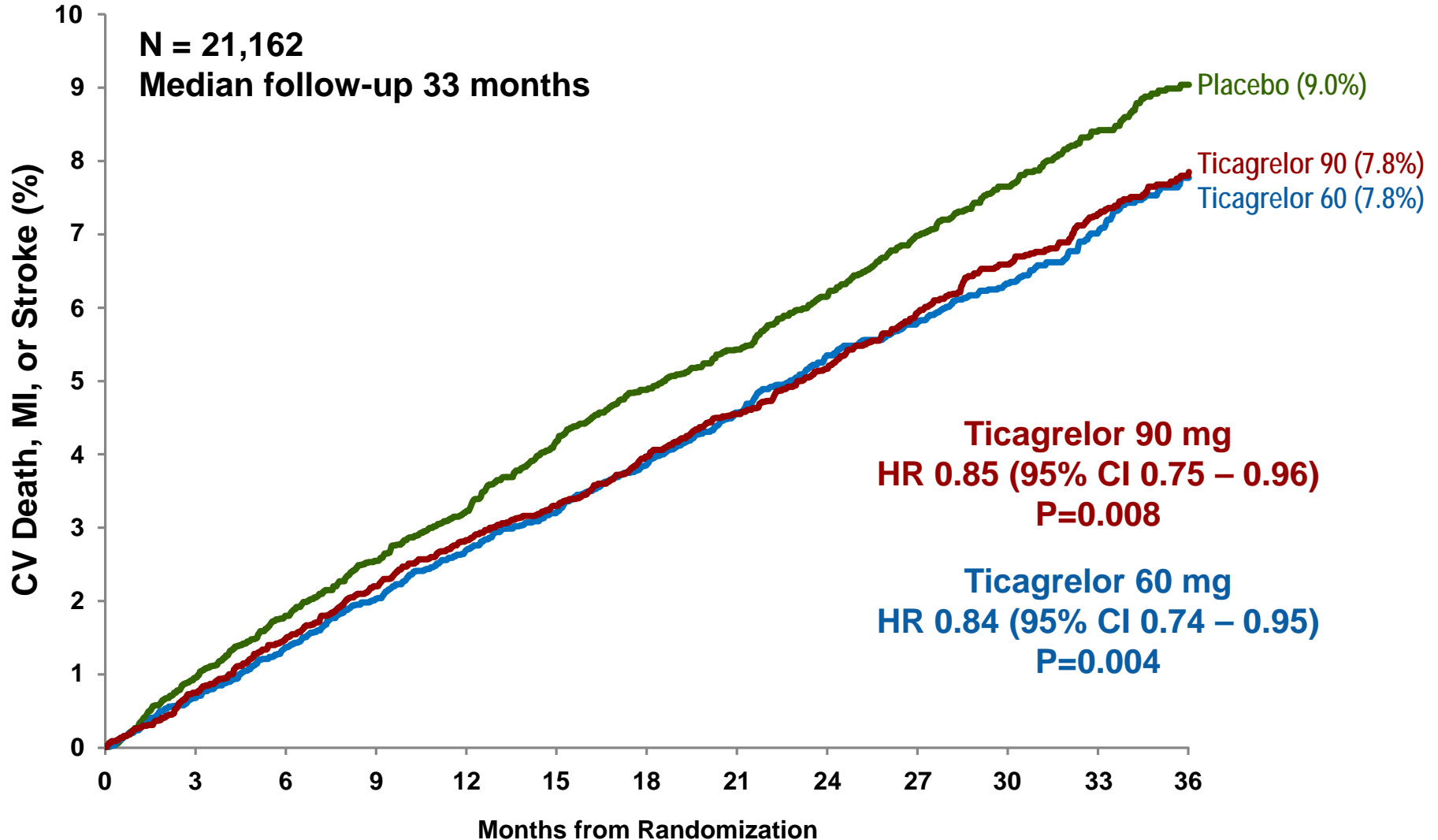


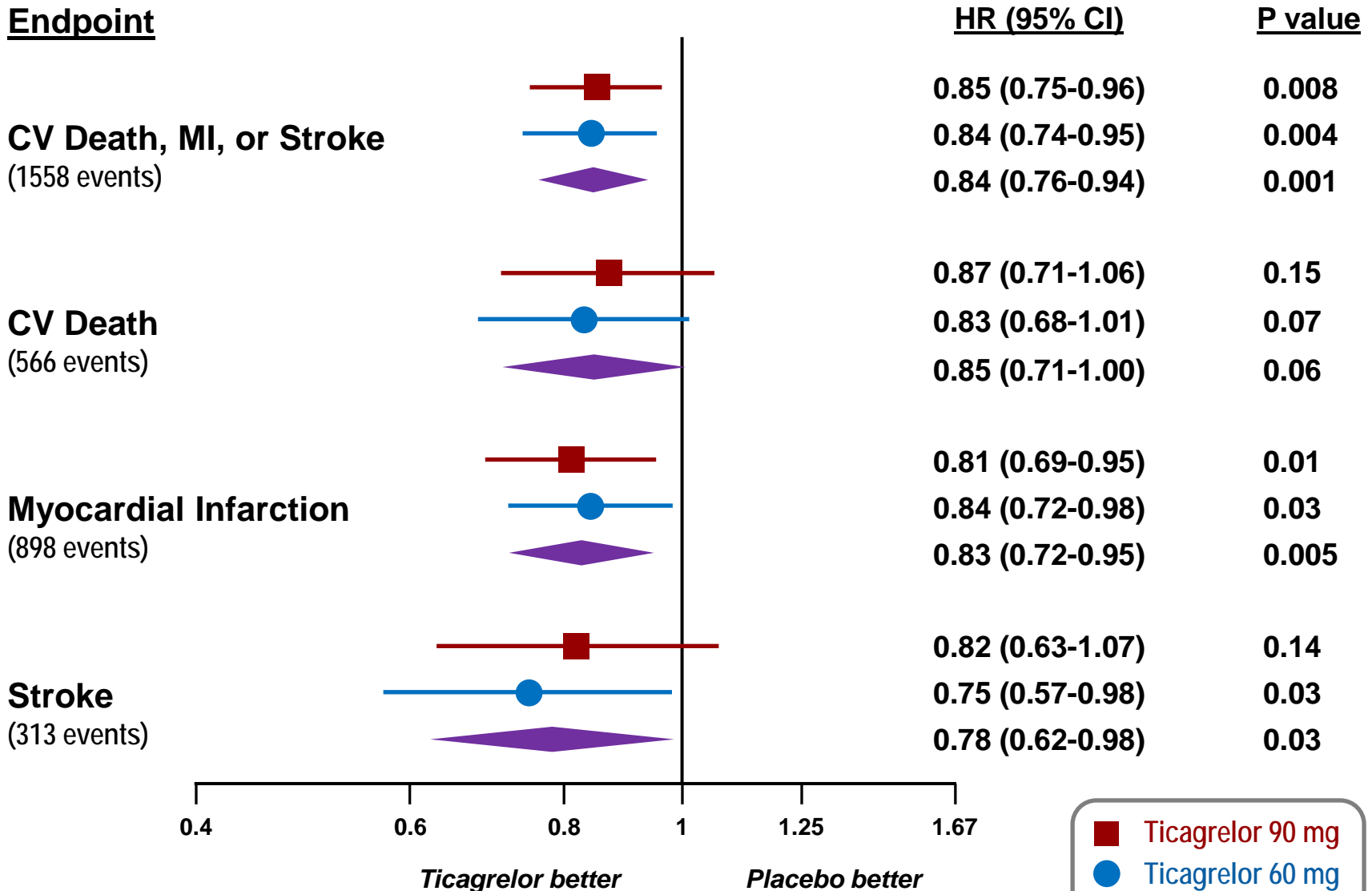
No difference between treatment arms.
Values for categorical variables are %.

Characteristic	Value
<i>Qualifying Event</i>	
Years from MI – median (IQR)	1.7 (1.2 – 2.3)
History of STEMI	53
History of NSTEMI	41
MI type unknown	6
<i>Medications at enrollment</i>	
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



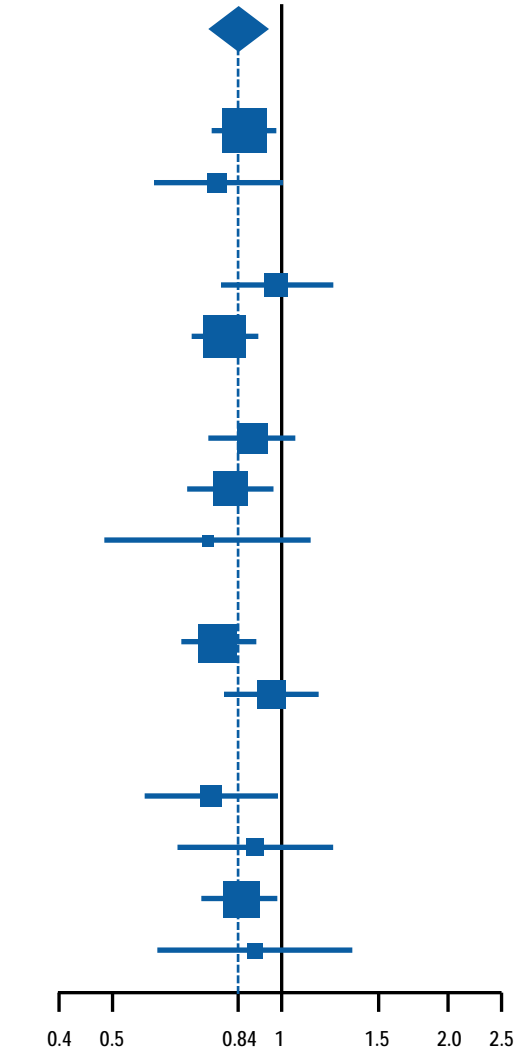
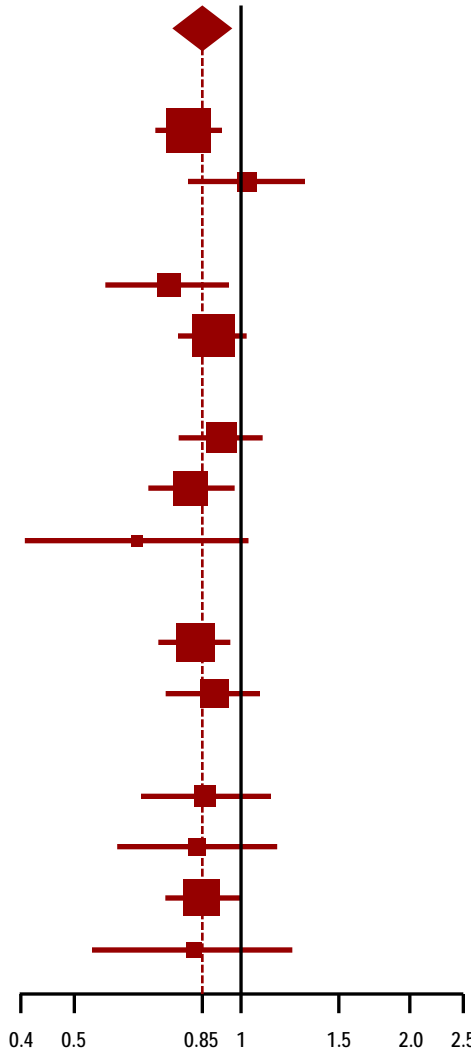


Outcome	Ticagrelor 90 mg bid (N=7050)	Ticagrelor 60 mg bid (N=7045)	Placebo (N=7067)	Ticagrelor 90 vs Placebo p-value	Ticagrelor 60 vs Placebo p-value
	3-yr KM rate (%)				
Coronary Death, MI, or Stroke	7.0	7.1	8.3	HR 0.82 P=0.002	HR 0.83 P=0.003
Coronary Death or MI	5.6	5.8	6.7	HR 0.81 P=0.004	HR 0.84 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

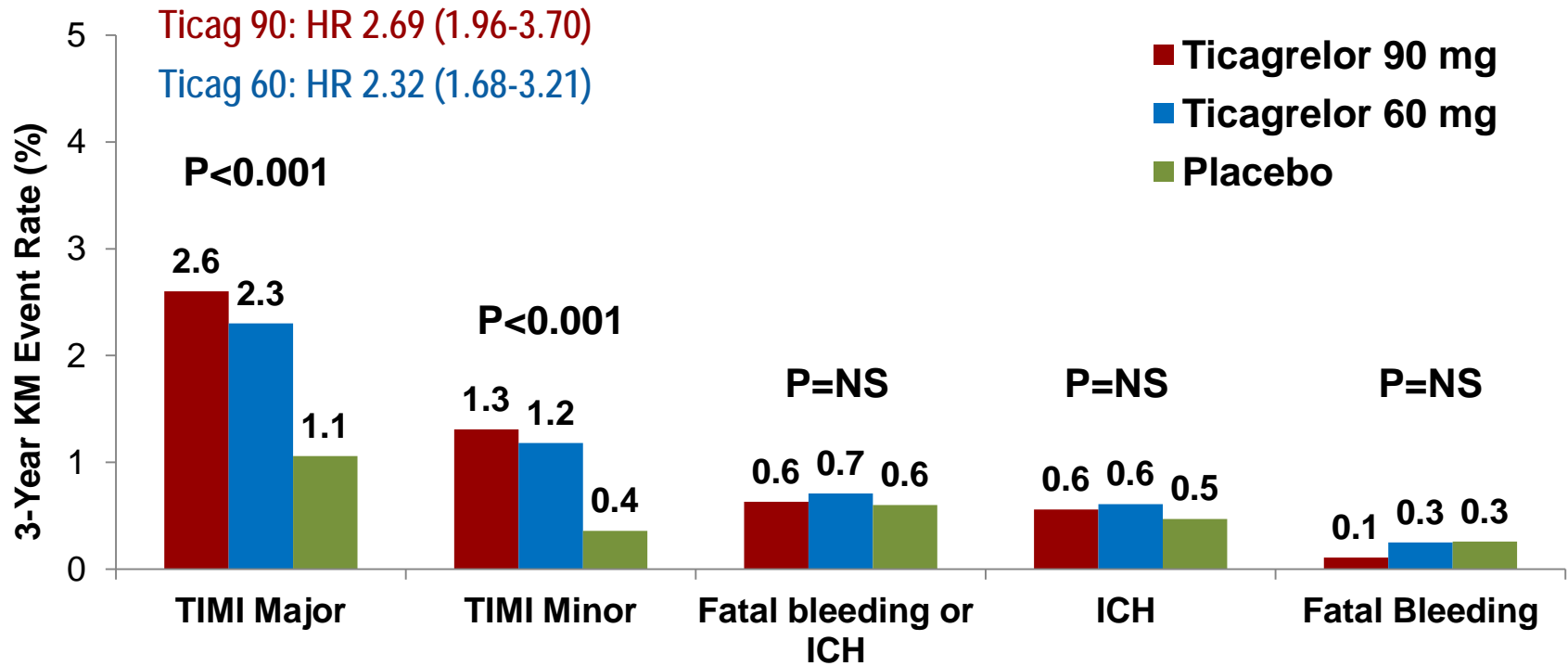
Hazard Ratio (95% CI)
Ticagrelor 90 mg vs Placebo

Hazard Ratio (95% CI)
Ticagrelor 60 mg vs Placebo

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



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

- **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**

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