Supplementary Online Content

Bonaca MP, Bhatt DL, Ophuis TO, et al. Long-term tolerability of ticagrelor for the secondary prevention of major adverse cardiovascular events: a secondary analysis of the PEGASUS-TIMI 54 trial. *JAMA Cardiol*. Published online June 15, 2016. doi:10.1001/jamacardio.2016.1017.

This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix
TIMI Bleeding Classification[2] (citation Bonaca et. al AHJ 2014)
Major:

1) Any intracranial* bleeding, *OR*

2) Clinically overt signs of hemorrhage associated with a drop in hemoglobin (Hgb) of ≥5 g/dL (or, when hemoglobin is not available, a fall in hematocrit of ≥15%),

OR

3) Fatal bleeding **(**a bleeding event that directly led to death within 7 days)

Minor: Any clinically overt sign of hemorrhage (including imaging) that is associated with a fall in Hgb of 3 to < 5 g/dL (or, when hemoglobin is not available, a fall in hematocrit of 9 to < 15%)

Note: To account for transfusions, Hgb measurements will be adjusted for any packed red blood cells (PRBCs) or whole blood given between baseline and post-transfusion measurements. A transfusion of one unit of blood will be assumed to result in an increase by 1 gm/dL in Hgb. Thus, to calculate the true change in hemoglobin, if there has been an intervening transfusion between two blood measurements, the following calculations should be performed:

$$\Delta \text{ Hgb} = [\text{Baseline Hgb} - \text{Post transfusion Hgb}] + [\#\text{ transfused units}]$$

$$\Delta \text{ Hematocrit} = [\text{ Baseline Hct} - \text{post transfusion Hct}] + [\text{number of transfused units} \times 3]$$

Medical Attention: Any overt sign of hemorrhage that meets one of the following criteria and that does not meet criteria for a major or minor bleeding event, as defined above.

- Requiring Intervention: defined as medical practitioner-guided medical or surgical treatment to stop or treat bleeding including temporarily or permanently discontinuing or changing the dose of a medication or study drug
- Leading to Hospitalization: defined as leading to or prolonging hospitalization
- Prompting Evaluation: defined as leading to unscheduled contact with a healthcare professional and diagnostic testing (laboratory or imaging)

Minimal: Any overt bleeding event that does not meet the criteria above.

eTable 1. Baseline Characteristics

Variable	Patients who Stopped Study Drug Prematurely N=5,728	Patients who Continued Study Drug N=15,214	P value
Demographics			
Age, median(IQR)	67 (61 – 73)	65 (58 – 70)	<0.001
Female, n (%)	1,596 (28)	3,407 (22)	<0.001
Caucasian*, n (%)	5,107 (89)	13,044 (86)	<0.001
BMI, median (IQR)	28 (25 – 32)	28 (25 – 31)	<0.001
Clinical Characteristics			
Hypertension, n (%)	4,565 (80)	11,673 (77)	<0.001
Hyperlipidemia, n (%)	4,487 (78)	11,593 (76)	0.0012
Current smoker, n (%)	963 (17)	2,541 (17)	0.85
Diabetes mellitus, n (%)	1,922 (34)	4,813 (32)	0.008
Multivessel CAD, n (%)	3,248 (57)	9,175 (60)	<0.001
PCI for Index MI, n (%)	4,814 (84)	12,565 (83)	0.013
Qualifying MI ≥ 2 years prior, n (%)	2,293 (40)	5,785 (38)	0.0076
History of more than 1 prior MI, n (%)	1,007 (18)	2,454 (16)	0.012
History of Spont. Bleeding, n (%)	92 (1.6)	172 (1.1)	0.006
eGFR at baseline <60 ml/min**, n (%)	1,647 (29)	3,141 (21)	<0.001
Last dose of $P2Y_{12}$ inhibitor ≤ 30 days prior to randomization	1,809 (36)	5,285 (39)	<0.001
Region			<0.001
Western Europe, n (%)	1,933 (34)	4,123 (27)	
Eastern Europe, n (%)	1,498 (26)	4,751 (31)	
North America, n (%)	1340 (23)	2,525 (17)	
South America, n (%)	484 (8)	1955 (13)	
Asia/Pacific, n (%)	473 (8)	1860 (12)	
Qualifying Event			<0.001
STEMI, n (%)	2,913 (51)	8,303 (55)	
NSTEMI, n (%)	2,448 (43)	6,048 (40)	
MI type unknown, n (%)	360 (6.3)	847 (5.6)	

**Self Reported*

***The estimated glomerular filtration rate was calculated with the use of the Modification of Diet in Renal Disease equation.*

eTable 2. Baseline Characteristics by Treatment in Patients who Never Stopped Study Treatment

Variable	Placebo	Ticagrelor 90 mg Twice Daily	Ticagrelor 60 mg Twice Daily	P value
	N=5,500	N=4,755	N=4,959	
Demographics				
Age, median(IQR)	65 (59 – 71)	64 (58 – 70)	64 (58 – 70)	<0.001¥
Female, n (%)	1,285 (23)	1,033 (22)	1,089 (22)	0.094
Caucasian*, n (%)	4,727 (86)	4,078 (86)	4,239 (86)	0.92
BMI, median (IQR)	28 (25 – 31)	28 (25 – 31)	28 (25 – 31)	0.50
Clinical Characteristics				
Hypertension, n (%)	4,242 (77)	3,638 (77)	3,793 (77)	0.68
Hyperlipidemia, n (%)	4,221 (77)	3,622 (76)	3,750 (76)	0.40
Current smoker, n (%)	874 (16)	810 (17)	857 (17)	0.12
Diabetes mellitus, n (%)	1,711 (31)	1,481 (31)	1,621 (33)	0.15
Multivessel CAD, n (%)	3,334 (61)	2,872 (60)	2,969 (60)	0.74
PCI for Index MI, n (%)	4,556 (83)	3,898 (82)	4,111 (83)	0.40
Qualifying MI ≥ 2 years prior, n (%)	2115 (39)	1,796 (38)	1,874 (38)	0.70
History of more than 1 prior MI, n (%)	902 (16)	754 (16)	798 (16)	0.75
History of Spont. Bleeding, n (%)	73 (1.3)	45 (0.9)	54 (1.1)	0.18
eGFR at baseline <60 ml/min**, n (%)	1,185 (22)	1,005 (21)	951 (19)	0.0068€
Last dose of $P2Y_{12}$ inhibitor ≤ 30 days prior to randomization	1894 (39)	1,663 (40)	1,728 (39)	0.75
Region				0.65
Western Europe, n (%)	1,521 (27)	1,258 (27)	1,344 (27)	
Eastern Europe, n (%)	1,677 (12)	1,523 (32)	1,551 (31)	
North America, n (%)	943 (17)	761 (16)	821 (17)	
South America, n (%)	696 (13)	623 (13)	636 (13)	
Asia/Pacific, n (%)	663 (12)	590 (12)	607 (12)	
Qualifying Event				0.62
STEMI, n (%)	2,994 (55)	2,610 (55)	2,699 (55)	
NSTEMI, n (%)	2,189 (40)	1,896 (40)	1,963 (40)	
MI type unknown, n (%)	310 (7)	245 (5)	592 (6)	

**Self Reported, **The estimated glomerular filtration rate was calculated with the use of the Modification of Diet in Renal Disease equation, ¥ significant differences were found for both 90mg and 60mg compared to placebo group (both p-values <0.01), € significant difference was found for 60mg compared to placebo group (p=0.0028).*

eTable 3. Reasons for Treatment Discontinuation by Treatment Arm

	Placebo	Ticagrelor 90 mg twice daily	Ticagrelor 60 mg twice daily
	N=6,996	N=6,988	N=6,958
Total Patients (% of total population)	1496 (21)	2233 (32)	1999 (29)
Discontinuation for an Event*	784 (11)	1434 (21)	1257 (18)
Discontinuation for an Ischemic Event	163 (2.3)	108 (1.6)	118 (1.7)
Discontinuation for Adverse Event**	621 (9)	1326 (19)	1139 (16)
Bleeding	86 (1.2)	453 (6.5)	354 (5.1)
Dyspnea	51 (0.7)	430 (6.2)	297 (4.3)
Arrhythmia	96 (1.4)	78 (1.1)	103 (1.5)
Renal AE	8 (0.1)	11 (0.2)	10 (0.1)
Bradycardia AE	2 (<0.1%)	4 (0.1)	4 (0.1)
Gout AE	4 (0.1)	3 (0)	1 (0)
Patient Decision	590 (8)	689 (10)	635 (9)
Protocol Issues	61 (1)	67 (1)	61 (1)
Other	61 (1)	43 (1)	46 (1)

**Includes efficacy and safety events **Patients could discontinue for more than 1 AE, therefore the categories are not mutually exclusive.*

eTable 4. Efficacy and Safety of Ticagrelor–On Treatment*

End Point	Placebo (N=6,996) n (%)	Ticagrelor Pooled (N=13,946) n (%)	Ticagrelor 90 mg bid (N=6,988) n (%)	Ticagrelor 60 mg bid (N=6,958) n (%)	Ticagrelor Pooled vs Placebo HR (95% CI) p-value	Ticagrelor 90 mg bid vs Placebo HR (95% CI) p-value	Ticagrelor 60 mg bid vs Placebo HR (95% CI) p-value
Efficacy							
CV Death, Myocardial Infarction, Stroke	465 (8.4)	659 (6.7)	322 (6.6)	337 (6.8)	0.78 (0.70 - 0.88) <0.001	0.79 (0.68 - 0.91) <0.001	0.78 (0.68 - 0.90) <0.001
CV Death	129 (2.4)	176 (1.9)	88 (1.9)	88 (1.8)	0.76 (0.61 - 0.96) 0.019	0.78 (0.60 - 1.03) 0.076	0.74 (0.57 - 0.97) 0.031
Cor. Heart Dis. Death	90 (1.6)	119 (1.3)	59 (1.3)	60 (1.2)	0.74 (0.56 - 0.97) 0.029	0.75 (0.54 - 1.04) 0.087	0.72 (0.52 - 1.00) 0.052
Myocardial Infarction	274 (4.9)	394 (4.0)	188 (3.8)	206 (4.1)	0.80 (0.68 - 0.93) 0.0036	0.78 (0.65 - 0.94) 0.0080	0.81 (0.68 - 0.97) 0.024
Stroke	98 (1.8)	132 (1.4)	66 (1.4)	66 (1.4)	0.75 (0.58 - 0.97) 0.029	0.77 (0.56 - 1.05) 0.094	0.73 (0.53 - 1.00) 0.048
All Cause Mortality	162 (3.1)	230 (2.4)	115 (2.5)	115 (2.3)	0.79 (0.65 - 0.97) 0.023	0.81 (0.64 - 1.03) 0.093	0.77 (0.61 - 0.98) 0.034

**Patients who received at least one dose of study drug, events occurring on or within 7 days of the last dose of study drug*

eTable 5. Efficacy and Safety of Ticagrelor–On Treatment with 30 Day Sensitivity*

End Point	Placebo (N=6,996) n (%)	Ticagrelor Pooled (N=13,946) n (%)	Ticagrelor 90 mg bid (N=6,988) n (%)	Ticagrelor 60 mg bid (N=6,958) n (%)	Ticagrelor Pooled vs Placebo HR (95% CI) p-value	Ticagrelor 90 mg bid vs Placebo HR (95% CI) p-value	Ticagrelor 60 mg bid vs Placebo HR (95% CI) p-value
Efficacy							
CV Death, Myocardial Infarction, Stroke	484 (8.6)	706 (7.0)	343 (6.9)	363 (7.1)	0.80 (0.72 - 0.9) < 0.001	0.80 (0.7 - 0.92) 0.0016	0.81 (0.7 - 0.93) 0.0021
CV Death	150 (2.8)	210 (2.2)	107 (2.3)	103 (2.1)	0.78 (0.63 - 0.96) 0.019	0.82 (0.64 - 1.04) 0.11	0.74 (0.58 - 0.96) 0.021
Cor. Heart Dis. Death	100 (1.8)	134 (1.4)	66 (1.5)	68 (1.4)	0.74 (0.57 - 0.96) 0.025	0.75 (0.55 - 1.03) 0.073	0.74 (0.54 - 1) 0.051
Myocardial Infarction	282 (5.0)	413 (4.1)	195 (3.9)	218 (4.3)	0.81 (0.69 - 0.94) 0.005	0.78 (0.65 - 0.94) 0.008	0.83 (0.7 - 0.99) 0.041
Stroke	103 (1.9)	143 (1.4)	70 (1.4)	73 (1.4)	0.77 (0.6 - 0.99) 0.042	0.77 (0.57 - 1.04) 0.091	0.77 (0.57 - 1.03) 0.083
All Cause Mortality	201 (3.8)	286 (3.0)	146 (3.1)	140 (2.8)	0.79 (0.66 – 0.95) 0.011	0.83 (0.67 – 1.03) 0.89	0.76 (0.61 – 0.94) 0.011

**Patients who received at least one dose of study drug, events occurring on or within 30 days of the last dose of study*

eTable 6. Efficacy of Ticagrelor–Modified On Treatment*

	Placebo			Ticagrelor (pooled)			Ticagrelor 90 mg			Ticagrelor 60 mg			Ticagrelor (pooled)		Ticagrelor 90 mg		Ticagrelor 60 mg	
	n	N	KM event rate	n	N	KM event rate	n	N	KM event rate	n	N	KM event rate	Hazard ratio	p-value	Hazard ratio	p-value	Hazard ratio	p-value
CVD/MI/stroke	471	6996	8.5%	707	13946	6.9%	349	6988	6.8%	358	6958	6.9%	0.80 (0.71-0.90)	<0.001	0.80 (0.70-0.92)	0.001	0.79 (0.69-0.91)	0.001
CV death	134	6996	2.5%	195	13946	2.0%	100	6988	2.0%	95	6958	1.9%	0.78 (0.62-0.97)	0.023	0.81 (0.62-1.05)	0.106	0.74 (0.57-0.97)	0.027
CHD death	92	6996	1.6%	130	13946	1.3%	66	6988	1.4%	64	6958	1.2%	0.75 (0.58-0.98)	0.037	0.78 (0.57-1.06)	0.116	0.73 (0.53-1.00)	0.053
MI	277	6996	5.0%	420	13946	4.1%	201	6988	3.9%	219	6958	4.2%	0.80 (0.69-0.94)	0.005	0.78 (0.65-0.94)	0.008	0.83 (0.69-0.99)	0.035
Stroke	99	6996	1.8%	141	13946	1.4%	72	6988	1.4%	69	6958	1.4%	0.76 (0.59-0.98)	0.034	0.79 (0.58-1.06)	0.119	0.73 (0.54-0.99)	0.045
All-cause death	174	6996	3.3%	285	13946	2.8%	147	6988	3.0%	138	6958	2.7%	0.87 (0.72-1.05)	0.156	0.91 (0.73-1.14)	0.425	0.83 (0.67-1.04)	0.106

**Patients who received at least one dose of study drug, events occurring on or within 7 days of the last dose of study except for patients who stopped due to bleeding at any time for whom all events through follow up are included.*

eTable 7. Propensity Score–Adjusted Outcomes with Ticagrelor

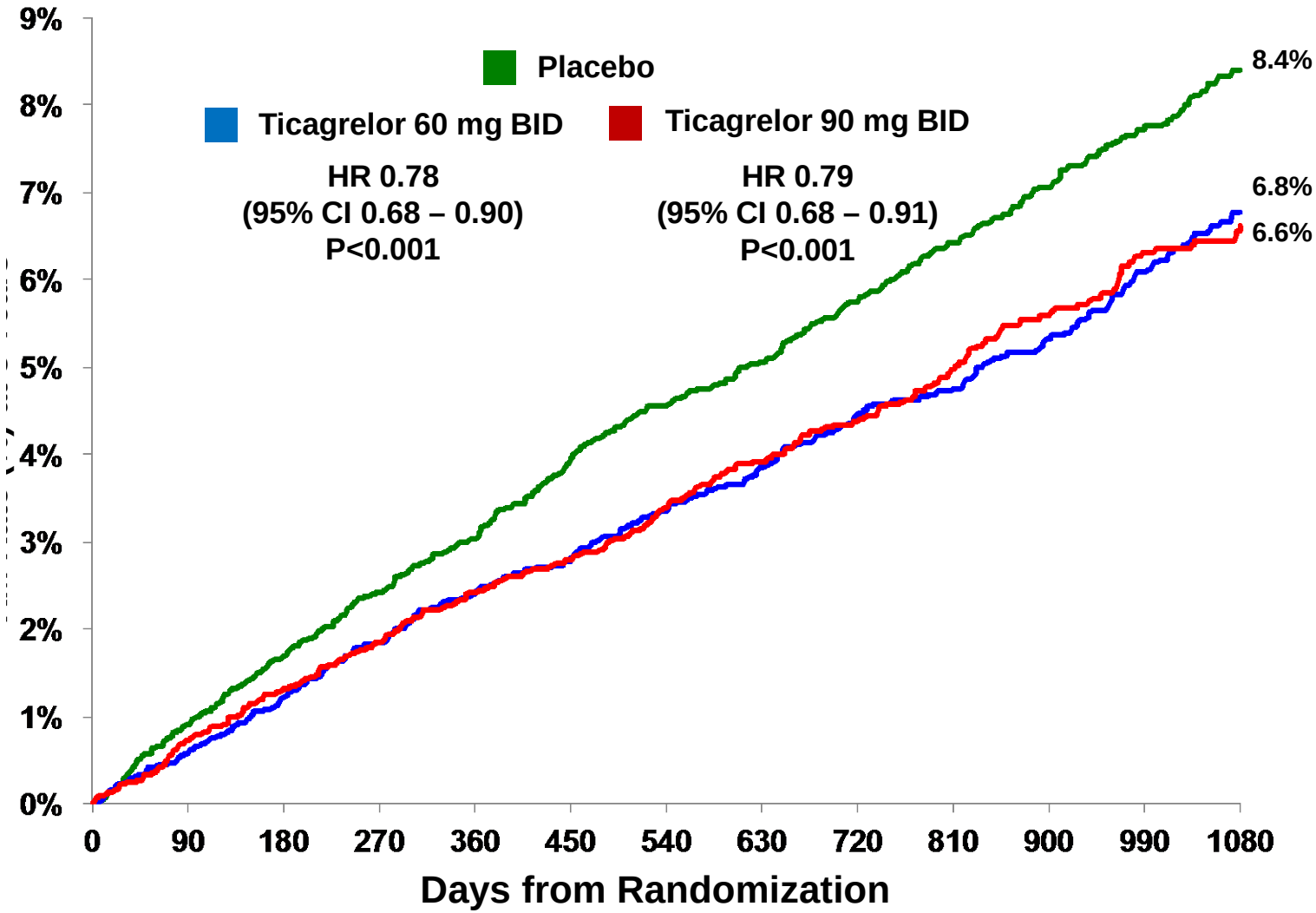
Efficacy of Ticagrelor (on treatment) after adjusting for propensity score for drug discontinuation

End Point	Ticagrelor Pooled vs. Placebo		Ticagrelor 90mg vs. Placebo		Ticagrelor 60mg vs. Placebo	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
CVD/MI/Stroke	0.75 (0.66, 0.86)	<.0001	0.71 (0.6, 0.84)	<.0001	0.79 (0.68, 0.93)	0.0052
CVD	0.67 (0.5, 0.89)	0.0052	0.62 (0.44, 0.89)	0.0089	0.7 (0.5, 0.99)	0.0408
CHD death	0.59 (0.42, 0.84)	0.0028	0.56 (0.37, 0.86)	0.0087	0.62 (0.41, 0.93)	0.0215
MI	0.77 (0.64, 0.91)	0.0031	0.69 (0.55, 0.85)	0.0007	0.84 (0.69, 1.03)	0.0972
Stroke	0.76 (0.56, 1.04)	0.0825	0.8 (0.56, 1.15)	0.2368	0.72 (0.5, 1.05)	0.0854
All death	0.74 (0.57, 0.94)	0.0158	0.73 (0.54, 0.99)	0.0398	0.74 (0.55, 0.99)	0.0448

Propensity model (c-index=0.639) included the variables: Age (<65, 65-75, >75), Sex, Region, Weight (Kg), eGFR <60, diabetes mellitus, hypertension, atrial fibrillation, COPD, Stroke/TIA, prior CABG, history of PCI, time from last ADP (<=30d, >30-1yr, >1yr)

All models met the proportional hazards assumption with the exception of stroke which had relatively few events

eFigure. Efficacy of Ticagrelor–On Treatment



The cumulative incidence of the composite of cardiovascular death, myocardial infarction and stroke with ticagrelor 90 mg (red) ticagrelor 60 mg (blue) and placebo (green) including events occurring on treatment or within 7 days of the last dose.