

Supplementary Online Content

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

eAppendix 1. Major bleeding ICD-10 codes

Intracranial bleed: I60.0-I60.9, I61.0-I61.6, I61.8, I61.9, I62.0, I62.1, I62.9

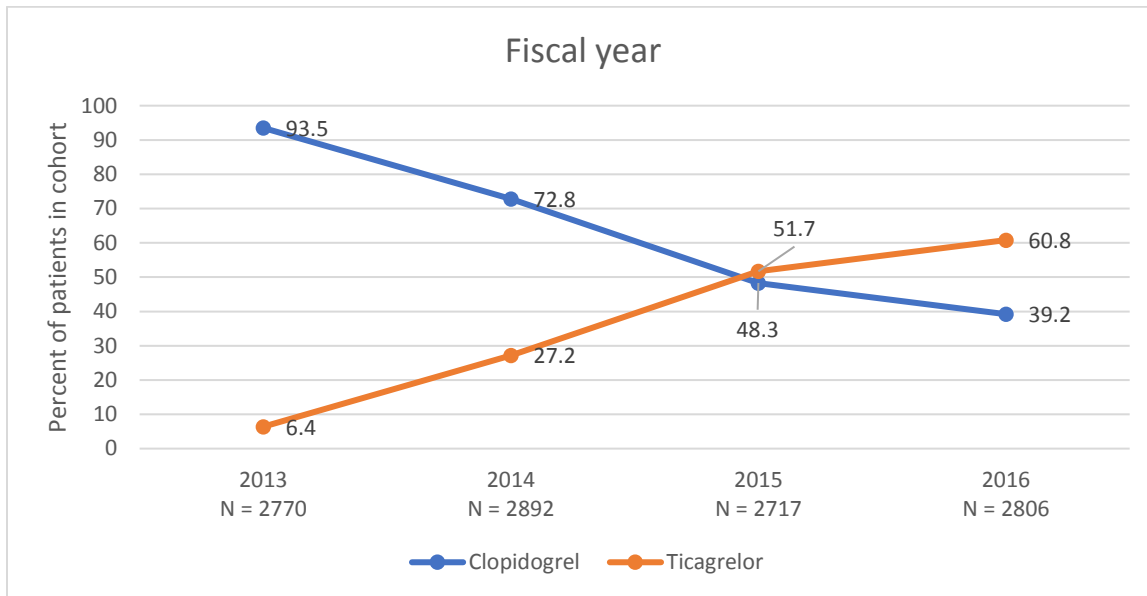
Gastrointestinal bleed: I85.0, I98.3, K22.1, K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K29.0, K62.5, K66.1, K92.0, K92.1, K92.2

Pulmonary bleed: R040, R041, R042, R048, R049

Urologic bleed: N02.0-N02.9, R31.0, R31.1, R31.8

Other bleed: R58, T810

eFigure. Study drug by fiscal year



eTable 1. Baseline characteristics by antiplatelet group in propensity score-matched cohort

Characteristic	Clopidogrel (n=3711)	Ticagrelor (n=3711)	Standardized difference
Age, median (IQR), years	61 (53, 71)	61 (54, 69)	-0.0525
Female, No. (%)	905 (24.4)	859 (23.1)	-0.0291
ACS type, No. (%)			0.0333
STEMI	1564 (42.1)	1604 (43.2)	
NSTEMI	1567 (42.2)	1537 (41.4)	
Unstable Angina	559 (15.1)	542 (14.6)	
Unknown	21 (0.6)	28 (0.8)	
Cardiovascular history and risk factors, No. (%)			
Prior MI	313 (8.4)	284 (7.7)	-0.0287
Prior CABG	167 (4.5)	161 (4.3)	-0.0079
Prior PCI	471 (12.7)	443 (11.9)	-0.023
Cerebrovascular disease	120 (3.2)	118 (3.2)	-0.0031
Peripheral vascular disease	154 (4.1)	135 (3.6)	-0.0265
Heart failure	136 (3.7)	123 (3.3)	-0.0191
Diabetes mellitus	929 (25.0)	891 (24.0)	-0.0238
Hyperlipidemia	2030 (54.7)	1963 (52.9)	-0.0362
Hypertension	2441 (65.8)	2362 (63.6)	-0.0446
Smoking status			0.0358
Current	1016 (27.4)	1005 (27.1)	
Former	730 (19.7)	684 (18.4)	
Never/not recorded	1965 (53.0)	2022 (54.5)	
Other comorbidities, No. (%)			
Chronic pulmonary disease	163 (4.4)	146 (3.9)	-0.0229
Renal disease	122 (3.3)	106 (2.9)	-0.025
Dialysis dependence	16 (0.4)	13 (0.4)	-0.013
Liver disease	12 (0.3)	15 (0.4)	0.0134
Malignancy	88 (2.4)	89 (2.4)	0.0018
Coronary Anatomy, No. (%)			0.0211
1 vessel	1197 (32.3)	1215 (32.7)	
2 vessels	1011 (27.2)	999 (26.9)	
2 vessels including proximal LAD	292 (7.9)	275 (7.4)	
3 vessels	583 (15.7)	589 (15.9)	
3 vessels including proximal LAD	490 (13.2)	495 (13.3)	
Left main	127 (3.4)	128 (3.4)	
Minimal CAD	11 (0.3)	10 (0.3)	
Ejection fraction, No. (%)			0.0298
>50	1242 (33.5)	1222 (32.9)	
35-50	489 (13.2)	460 (12.4)	
20-34	57 (1.5)	59 (1.6)	

<20	4 (0.1)	4 (0.1)	
Missing	1919 (51.7)	1966 (53.0)	
Stent placement, No. (%)	3485 (93.9)	3486 (93.9)	0.0011
Drug-eluting stent, No. (%)	2761 (74.4)	2789 (75.2)	0.0174
Laboratory values, median (IQR)			
Hemoglobin, g/L	139 (128, 149)	141 (129, 150)	0.0489
Serum creatinine, umol/L	82 (71, 95)	85 (73, 97)	0.0098
eGFR, mL/min	76 (61, 91)	79 (64, 92)	0.0746
Medications within 31 days, No. (%)			
Oral anticoagulant	121 (3.3)	134 (3.6)	0.0192
Proton pump inhibitor	1159 (31.2)	1163 (31.3)	0.0023

ACS: Acute coronary syndrome; CABG: Coronary artery bypass grafting; eGFR: Estimated glomerular filtration rate; MI: Myocardial infarction; NSTEMI: Non-ST-segment elevation myocardial infarction; PCI: Percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction.

eTable 2. Major adverse coronary events within 1 year after percutaneous coronary intervention for acute coronary syndrome adjusted for the Cardiac-Specific Comorbidity Index

Outcome	HR (95% CI) adjusted for CSCI^a
MACE	0.91 (0.80 - 1.03)
All-cause death	0.99 (0.73 - 1.34)
ACS	0.89 (0.76 - 1.04)
Coronary revascularization	0.88 (0.72 - 1.06)
PCI	0.89 (0.71 - 1.12)
CABG	0.82 (0.55 - 1.21)
Stent thrombosis	1.31 (0.71 - 2.42)
Composite of all-cause death, ACS, ischemic stroke	0.90 (0.79 - 1.04)

^aTicagrelor compared to clopidogrel (reference).

ACS: Acute coronary syndrome; CABG: Coronary artery bypass grafting; CI: Confidence interval; CSCI: Cardiac-Specific Comorbidity Index; HR: Hazard ratio; MACE: Major adverse coronary event; PCI: Percutaneous coronary intervention.

eTable 3. Subgroup analyses

Subgroup	No. in Subgroup	aHR for MACE	aHR for Major Bleed	aHR for Dyspnea
Age				
<65	6572	0.94 (0.79 - 1.12)	1.50 (1.17 - 1.94)	1.63 (1.02 - 2.6)
65-74	2625	1.03 (0.80 - 1.33)	1.51 (1.13 - 2.02)	2.42 (1.45 - 4.06)
≥75	1988	0.97 (0.73 - 1.28)	1.54 (1.12 - 2.10)	1.80 (1.02 - 3.15)
Diabetes				
Yes	2775	0.93 (0.74 - 1.16)	1.50 (1.08 - 2.08)	2.45 (1.48 - 4.04)
No	8410	0.98 (0.84 - 1.15)	1.52 (1.26 - 1.83)	1.78 (1.24 - 2.56)
eGFR, mL/min				
≥60	9177	0.96 (0.83 - 1.11)	1.50 (1.24 - 1.81)	2.09 (1.47 - 2.95)
<60	1868	0.99 (0.75 - 1.30)	1.56 (1.14 - 2.15)	1.67 (0.94 - 2.96)
High-risk ACS per PLATO criteria				
Yes	8862	1.02 (0.89 - 1.18)	1.57 (1.31 - 1.89)	1.89 (1.36 - 2.63)
No	2323	0.78 (0.58 - 1.05)	1.29 (0.89 - 1.88)	2.48 (1.28 - 4.82)
TIMI Risk Score for Secondary Prevention				
≥3	2784	0.88 (0.70 - 1.12)	1.83 (1.38 - 2.44)	2.11 (1.31 - 3.38)
<3	8401	1.00 (0.86 - 1.16)	1.38 (1.13 - 1.68)	1.88 (1.29 - 2.73)
Fiscal year of index PCI				
2013-2014	5662	0.94 (0.75 - 1.17)	1.77 (1.36 - 2.32)	2.06 (1.24 - 3.43)
2015-2016	5523	0.97 (0.82 - 1.15)	1.34 (1.07 - 1.69)	1.89 (1.33 - 2.71)
Excluding oral anticoagulant use within 31 days	9991	0.97 (0.85 - 1.10)	1.49 (1.25 - 1.77)	2.06 (1.50 - 2.84)
Excluding patients with atrial fibrillation	10376	0.97 (0.85 - 1.11)	1.53 (1.29 - 1.81)	2.19 (1.60 - 3.00)
Excluding patients who switched P2Y ₁₂ inhibitors	10452	0.98 (0.86 - 1.12)	1.40 (1.18 - 1.66)^a	1.27 (0.90 - 1.78) ^a

Comparison of ticagrelor compared to clopidogrel, i.e. values below 1.00 indicate lower risk of the outcome with ticagrelor than clopidogrel. Statistically significant results are shown in bold text.

^a This analysis did not distinguish regarding time of the switch relative to the outcome event (i.e. this analysis excludes participants who switched P2Y₁₂ inhibitors subsequent to an outcome event).

aHR compares ticagrelor to clopidogrel (reference group) using adjusted model 2 in Table 2.

aHR: Adjusted hazard ratio; eGFR: Estimated glomerular filtration rate; MACE: Major adverse coronary event; PLATO: Platelet Inhibition and Patient Outcomes; TIMI: Thrombolysis in Myocardial Infarction.

eTable 4. Multivariate model for effectiveness and safety outcomes within 1 year after percutaneous coronary intervention for acute coronary syndrome

Variable	aHR (95% CI)	P value
Outcome = MACE		
Study drug (ref = clopidogrel)		
Ticagrelor	0.96 (0.85 - 1.09)	0.56

Age, per year	1.004 (0.999 - 1.010)	0.09
Female	1.01 (0.88 - 1.17)	0.85
Prior PCI	1.20 (1.02 - 1.41)	0.03
Diabetes mellitus	1.28 (1.12 - 1.45)	0.0002
Hyperlipidemia	0.85 (0.76 - 0.96)	0.01
Coronary anatomy (ref = 1 vessel)		
2 vessels	1.40 (1.18 - 1.66)	0.0001
2 vessels including proximal LAD	1.77 (1.4 - 2.24)	<.0001
3 vessels	1.80 (1.50 - 2.16)	<.0001
3 vessels including proximal LAD	2.24 (1.86 - 2.69)	<.0001
Left main	3.31 (2.58 - 4.26)	<.0001
Drug-eluting stent	0.73 (0.65 - 0.82)	<.0001
Hemoglobin, per 0.1 g/dL	0.989 (0.985 - 0.993)	<.0001
Serum creatinine, per 0.0113 mg/dL	1.001 (1.001 - 1.002)	<.0001
Proton pump inhibitor within 31 days	1.19 (1.06 - 1.34)	0.003
Outcome = Major bleed		
Study drug (ref = clopidogrel)		
Ticagrelor	1.48 (1.26 - 1.74)	<.0001
Age, per year	1.03 (1.02 - 1.04)	<.0001
Female	0.85 (0.71 - 1.02)	0.09
Malignancy	1.43 (1.03 - 1.99)	0.03
Hemoglobin, per 0.1 g/dL	0.985 (0.980 - 0.989)	<.0001
Serum creatinine, per 0.0113 mg/dL	1.002 (1.001 - 1.003)	0.0001
Oral anticoagulant within 31 days	2.12 (1.76 - 2.57)	<.0001
Outcome = Dyspnea		
Study drug (ref = clopidogrel)		
Ticagrelor	1.98 (1.48 - 2.65)	<.0001
Age, per year	1.03 (1.01 - 1.04)	<.0001
Female	1.25 (0.94 - 1.66)	0.12
Year of index PCI	1.22 (1.06 - 1.39)	0.005
Prior MI	1.48 (1.02 - 2.15)	0.04
Diabetes mellitus	1.44 (1.09 - 1.90)	0.01
Chronic pulmonary disease	2.62 (1.82 - 3.76)	<.0001
Renal disease	2.41 (1.56 - 3.72)	<.0001

aHR: Adjusted hazard ratio; CI: Confidence interval; LAD: Left anterior descending; MACE: Major adverse coronary event; PCI: Percutaneous coronary intervention.

eTable 5. Sensitivity analysis: Stepwise addition of covariates to multivariate analysis of ticagrelor versus clopidogrel on major adverse coronary events within 1 year after percutaneous coronary intervention for acute coronary syndrome

Model ^a	Adjusted HR (95% CI)
Unadjusted	0.84 (0.74 - 0.95)
Adjusted for age and sex	0.88 (0.78 - 0.995)
+ coronary anatomy	0.86 (0.76 - 0.97)
+ hemoglobin	0.90 (0.79 - 1.02)
+ drug-eluting stent	0.95 (0.84 - 1.08)
+ creatinine	0.96 (0.84 - 1.09)
+ diabetes mellitus	0.96 (0.85 - 1.09)
+ proton pump inhibitor within 31 days	0.97 (0.85 - 1.10)
+ hyperlipidemia	0.96 (0.85 - 1.09)
+ prior PCI	0.96 (0.85 - 1.09)

^a Each line includes variables from previous line plus additional variable indicated.

CI: Confidence interval; HR: Hazard ratio; PCI: Percutaneous coronary intervention