

Supplemental Material

Assessment of Impact of Patient Recruitment Volume on Risk Profile, Outcomes and Treatment Effect in a Randomized Trial of Ticagrelor vs. Prasugrel in Acute Coronary Syndromes

Brief title: Recruitment center and outcome

Authors: Gjini Ndrepepa, M.D.¹; Franz Josef Neumann, M.D.²; Maurizio Menichelli, M.D.³; Isabell Bernlochner, M.D.^{4,5}; Gert Richardt, M.D.⁶; Jochen Wöhrle, M.D.⁷; Bernhard Witzensbichler, M.D.⁸; Katharina Mayer, M.D.¹; Salvatore Cassese, M.D.¹, Ph.D.; Senta Gewalt, M.D.¹; Erion Xhepa, M.D.; Ph.D.¹; Sebastian Kufner, M.D.¹; Hendrik B. Sager, M.D.^{1,5}; Michael Joner, M.D.^{1,5}; Tareq Ibrahim, M.D.⁴; Karl Ludwig Laugwitz, M.D.^{4,5}; Heribert Schunkert, M.D.^{1,5}; Stefanie Schüpke, M.D.^{1,5}; Adnan Kastrati, M.D.^{1,5}

Affiliations:

¹Deutsches Herzzentrum München, Cardiology and Technische Universität München, Munich, Germany;

²Department of Cardiology and Angiology II, University Heart Center Freiburg · Bad Krozingen, Bad Krozingen, Germany;

³Ospedale Fabrizio Spaziani, Cardiology, Frosinone, Italy;

⁴Medizinische Klinik und Poliklinik Innere Medizin I (Kardiologie, Angiologie, Pneumologie), Klinikum rechts der Isar, Munich, Germany;

⁵German Center for Cardiovascular Research (DZHK), Partner Site Munich Heart Alliance, Germany;

⁶Heart Center Bad Segeberg, Bad Segeberg, Germany;

⁷Dept. of Cardiology, Medical Campus Lake Constance, Friedrichshafen, Germany;

⁸Helios Amper-Klinikum Dachau, Cardiology & Pneumology, Dachau, Germany

Corresponding author:

Adnan Kastrati, M.D.

Deutsches Herzzentrum München

Lazarettstrasse 36

80636 Munich, Germany

Phone: +49 (0) 89 1218 - 4578

E-mail: kastrati@dhm.mhn.de

Table S1. Angiographic characteristics

Characteristic	Low recruitment center (n=1006)	High recruitment center (n=2998)	P value
Access site			0.963
Femoral	663 (62.9)	1872 (62.4)	
Radial	368 (36.6)	1111 (37.1)	
Other	5 (0.5)	15 (0.5)	
Number of diseased coronary vessels			
No obstructive coronary artery disease	53 (5.3)	281 (9.4)	<0.001
One vessel	337 (33.5)	846 (28.2)	0.0015
Two vessels	309 (30.7)	767 (25.6)	0.0015
Three vessels	307 (30.5)	1104 (36.8)	<0.001
Left ventricular ejection fraction*	53.9±12.2	51.2±10.9	<0.001

Data are as counts (%) or mean ± standard deviation.

*Left ventricular ejection fraction was not available in 175 patients in the low recruitment center group and 49 patients in the high recruitment center group (17.4% vs. 1,6%; P<0.001)

Table S2. Procedural characteristics

Characteristic	Low recruitment center (n=903)	High recruitment center (n=2474)	P value
More than 1 lesion treated	270 (29.9)	903 (36.6)	<0.001
Target vessel			0.065
Left main coronary artery	15 (1.7)	59 (2.4)	
Left anterior descending coronary artery	360 (39.8)	1104 (44.6)	
Left circumflex coronary artery	196 (21.7)	495 (20.0)	
Right coronary artery	314 (34.8)	775 (31.3)	
Bypass graft	18 (2.0)	41 (1.7)	
Complex lesion (type B2/C)	454 (50.3)	1533 (62.0)	<0.001
TIMI flow grade before the intervention			<0.001
0	357 (39.5)	819 (33.1)	
1	85 (9.4)	197 (8.0)	
2	220 (24.4)	527 (21.3)	
3	241 (26.7)	931 (37.6)	
TIMI flow grade after the intervention			0.121
0	8 (0.9)	25 (1.0)	
1	5 (0.6)	11 (0.4)	
2	14 (1.5)	73 (3.0)	
3	876 (97.0)	2365 (95.6)	
Type of intervention			
Drug-eluting stent	853 (94.5)	2187 (88.4)	<0.001
Bare-metal stent	5 (0.6)	7 (0.3)	0.323
Bioresorbable vascular scaffold	26 (2.9)	169 (6.8)	<0.001
Drug-eluting balloon	14 (1.5)	49 (2.0)	0.500
Plain balloon angioplasty	19 (2.1)	83 (3.4)	0.077
Maximal stent diameter (mm)	3.24±0.52	3.17±0.49	0.001
Total stented length (mm)	30.1±17.5	30.7 ±16.7	0.430
Successful PCI	888 (98.3)	2414 (97.6)	0.229
Periprocedural antithrombotic medication			
Aspirin	787 (87.2)	2248 (90.9)	0.002
Unfractionated heparin	889 (98.4)	2288 (92.5)	<0.001
Low molecular weight heparin	33 (3.6)	106 (4.3)	0.473
Bivalirudin	5 (0.6)	261 (10.5)	<0.001
Glycoprotein IIb/IIIa inhibitor	152 (16.8)	265 (10.7)	<0.001

Data are shown as counts (%) or mean ± standard deviation; PCI= percutaneous coronary intervention; TIMI = Thrombolysis in Myocardial Infarction

Table S3. Diagnosis and Drug Therapy at Discharge*

Characteristic	Low recruitment center (n=1005)	High recruitment center (n=3005)	P value
Final diagnosis of ACS	951 (94.6)	2692 (89.6)	<0.001
Therapy at discharge†			
Aspirin	963/994 (96.9)	2781/2959 (94.0)	<0.001
Ticagrelor	439/984 (44.2)	1177/2959 (39.8)	0.017
Prasugrel	439/994 (44.2)	1178/2959 (39.8)	0.017
Clopidogrel	30/994 (3.0)	177/2959 (5.9)	<0.001
Oral anticoagulant drugs	35/994 (3.5)	147/2959 (5.0)	0.073
Beta blocker	831/994 (83.6)	2455/2959 (83.0)	0.680
ACE inhibitor/ARB	849/994 (85.4)	2500/2959 (84.5)	0.516
Statin	913/994 (91.9)	2728/2959 (92.2)	0.781

* Not available for patients who withdrew consent before discharge,

† Shown for patients discharged alive, not available for patients who withdrew consent

ACE=angiotensin converting enzyme; ACS=acute coronary syndrome; ARB=angiotensin receptor blocker

Table S4. Antithrombotic medication after discontinuation of ticagrelor or prasugrel during the follow-up

Characteristic	Low recruitment center (n=101)	High recruitment center (n=341)	P value
Ticagrelor	3 (3.0)	11 (3.2)	1.00
Prasugrel	10 (9.9)	25 (7.3)	0.529
Clopidogrel	49 (48.5)	176 (51.6)	0.664
Oral anticoagulation	19 (18.8)	65 (19.1)	1.00
None of the aforementioned medication	34 (33.7)	108 (31.7)	0.799
Study drug discontinuation time (day)*	109.0 [33.0-220.0]	90 [25.0-191.0]	0.238

Data are counts (%) or median [25th-75th percentiles]; Percentages refer to patients who discontinued the study drugs during follow-up

*Time interval from hospital discharge to drug discontinuation

Table S5. Reasons for discontinuation of the study drug in low recruitment and high recruitment centers

Reason	Low recruitment center (n=101)	High recruitment center (n=341)
Allergy	1 (1.0)	18 (5.3)
Allergy plus dyspnea	1 (1.0)	0
Bleeding	23 (22.8)	54 (15.8)
Bleeding plus dyspnea	1 (1.0)	1 (0.3)
Bradycardia	0	1 (0.3)
Coronary artery bypass surgery	1 (1.0)	22 (6.2)
Attending physician's decision	25 (24.8)	109 (32.0)
Glioblastoma	0	1 (0.3)
Thrombocytopenia	1 (1.0)	0
Dyspnea	13 (12.9)	28 (8.2)
Anemia	0	1 (0.3)
Stroke	1 (1.0)	4 (1.2)
Stroke plus indication for OAC	0	1 (0.3)
Indication for OAC	20 (19.8)	61 (17.9)
Indication for OAC plus dyspnea	1 (1.0)	0
Planned surgery	0	1 (0.3)
Incompliance	4 (4.0)	23 (6.7)
Unspecific side effects to SM	3 (3.0)	15 (4.4)
Unclear	5 (5.0)	2 (0.6)

Data are number of events (percentages)

OAC=oral anticoagulant; SM=study medication

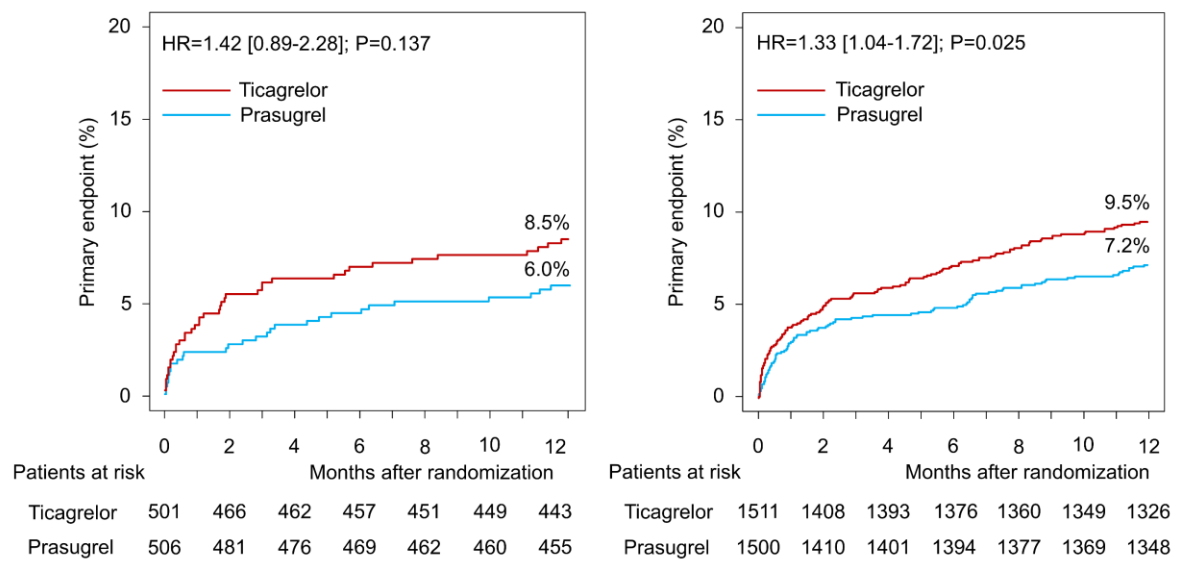


Figure S1. Primary endpoint (composite of all-cause death, myocardial infarction or stroke) in patients assigned to ticagrelor or prasugrel in low recruitment centers (left panel) and high recruitment centers (right panel).

HR=hazard ratio

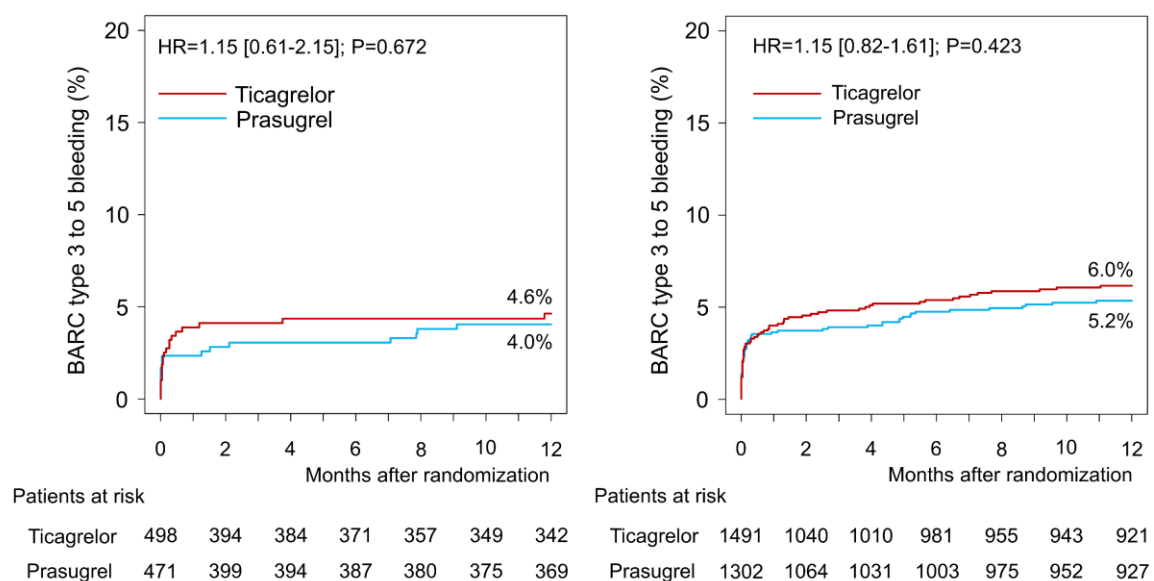


Figure S2. Secondary endpoint of bleeding in patients assigned to ticagrelor or prasugrel in low recruitment centers (left panel) and high recruitment centers (right panel).

BARC= Bleeding Academic Research Consortium; HR=hazard ratio