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ORIGINAL RESEARCH

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

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BACKGROUND: Whether there are differences in the risk profile and treatment effect in patients recruited in a low recruitment center (LRC) versus patients recruited in a high recruitment center (HRC) in a randomized multicenter trial remains unknown.

METHODS AND RESULTS: This study included 4018 patients with acute coronary syndrome recruited in the ISAR-REACT 5 (Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment 5) trial. The primary end point was a composite of all-cause death, myocardial infarction, or stroke. Overall, 3011 patients (75%) were recruited in the HRCs (7 centers recruiting 258 to 628 patients; median, 413 patients) and 1007 patients (25%) were recruited in the LRCs (16 centers recruiting 5 to 201 patients; median, 52 patients). Patients recruited in the LRCs had more favorable cardiovascular risk profiles than patients recruited in the HRCs. The primary end point occurred in 72 patients in the LRCs and 249 patients in the HRCs (cumulative incidence, 7.3% and 8.4%; P=0.267). All-cause mortality was lower among patients recruited in the LRCs (n=29) than among patients recruited in the HRCs (n=134; cumulative incidence 2.9% versus 4.5%; P=0.031). There was no significant interaction between the treatment effect of ticagrelor versus prasugrel and patient recruitment category (LRC versus HRC) regarding the primary efficacy end point (LRC: hazard ratio [HR], 1.42 [95% CI, 0.89–2.28]; HRC: HR, 1.33 [95% CI, 1.04–1.72]; P for interaction=0.800).

CONCLUSIONS: Patients with acute coronary syndrome recruited in a LRC appear to have more favorable cardiovascular risk profiles and lower 1-year mortality rates compared with patients recruited in a HRC. The recruitment volume did not interact with the treatment effect of ticagrelor versus prasugrel.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT01944800.

Key Words: mortality ■ prasugrel ■ randomized controlled trial ■ recruitment center ■ ticagrelor

See Editorial by Gaba and Bhatt.

Randomized controlled trials (RCTs) are widely accepted as the gold standard for the assessment of the efficacy and safety of newer therapies in clinical medicine.[1] By avoiding bias in patient selection, RCTs are considered the highest level of scientific evidence[2] and the apotheosis of scientific progress in

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CLINICAL PERSPECTIVE

What Is New?

- This study demonstrated that patients with acute coronary syndromes recruited in low recruitment centers have more favorable cardiovascular risk profiles and lower 1-year mortality rates than patients recruited in high recruitment centers.
- Recruitment volume did not impact the treatment effect of ticagrelor versus prasugrel regarding the composite end point of death, myocardial infarction or stroke, as well as stent thrombosis and major bleeding.

What Are the Clinical Implications?

- Because low recruitment centers appear to be prone to selection bias resulting in the enrollment of patients at lower cardiovascular risk, the center recruitment volume should be considered when designing and interpreting the results of randomized multicenter clinical studies of patients with acute coronary syndromes.

Nonstandard Abbreviations and Acronyms

BARC	Bleeding Academic Research Consortium
HRC	high recruitment center
LRC	low recruitment center

clinical medicine.[3] Single-center trials tend to provide larger treatment effects, and their results should be cautiously used for decision making.[4] Contemporary RCTs in cardiovascular medicine typically need the recruitment of a large number of patients to reach the study end points for the assessment of the efficacy and safety of newer interventions. Consequently, nearly all major trials in cardiology are multicenter studies adopting a global recruitment strategy.[5] Multicenter RCTs have greater credence and generalizability than single-center RCTs.[6] Although multicenter RCTs have advantages over single-center trials in many aspects, heterogeneity in clinical practice across the centers appears to be an important confounding factor when it comes to the interpretation of the findings of RCTs.[5] RCTs assessing the efficacy and safety of percutaneous coronary interventions (PCIs) face specific issues,[7] including the potential impact of center and operator volumes on the treatment effect.[8–10] RCTs differ widely with respect to the number of recruited patients in the trial, with some centers recruiting large numbers of patients and other centers recruiting a few patients. However, whether there are differences in the characterization of patients in terms of cardiovascular risk and the treatment effect in patients enrolled in a low recruitment center (LRC) versus those enrolled in a high recruitment center (HRC) in the setting of a RCT remains largely unknown. We undertook this study to assess whether there are differences in terms of patient characterization and clinical outcomes of patients enrolled in the LRC versus those recruited in the HRC in the setting of a recent RCT that assessed the efficacy and safety of new antiplatelet drug therapies in patients with acute coronary syndromes (ACSs) who were planned to undergo invasive therapy.

METHODS

Patients

The data that support the findings of this study are available from the corresponding author on reasonable request. Parties interested in collaboration and data sharing may contact the corresponding author directly. This study included 4018 patients assigned to receive ticagrelor or prasugrel in the ISAR-REACT 5 (Intracoronary Stenting and AntiThrombotic Regimen: Rapid Early Action for Coronary Treatment 5) trial.[11] The ISAR-REACT 5 trial included patients with ACS who planned to undergo an invasive management strategy. The trial had a randomized multicenter design with 23 participating centers in Germany (21 centers) and Italy (2 centers; 1 HRC and 1 LRC) with patients recruited between September 2013 and February 2018. The study design, inclusion and exclusion criteria, and outcomes are reported in the primary trial.[11] The study conforms to the Declaration of Helsinki, and the study protocol was approved by the local ethics committee at each participating center.

Procedures and Drugs

Patients were randomly assigned to receive ticagrelor (n=2012) or prasugrel (n=2006). Patients assigned to ticagrelor received a loading dose of 180 mg immediately after admission and continued with a maintenance dose of 90 mg twice daily. Patients presenting with ST-segment–elevation myocardial infarction assigned to prasugrel received the loading dose of prasugrel as soon as possible after admission. Patients presenting with non–ST-segment–elevation myocardial infarction or unstable angina assigned to prasugrel received a loading dose of 60 mg of prasugrel after the coronary anatomy was known (after coronary angiography but before PCI). In the prasugrel group, the maintenance daily dose was 10 mg, with adjustment to 5 mg for patients aged ≥75 years or those with a body weight of <60 kg.[12] Aspirin was used as a loading dose of 150 to 300 mg of intravenous or chewed aspirin and continued with a maintenance dose of 75 to 100 mg daily in all patients. Other drugs were prescribed at the discretion of the attending physician.

Study Definitions, End Points, and Follow-Up

In the current analysis, HRCs were defined as those belonging to the upper 30% of the centers with the highest number of recruited patients. Applying this criterion, in the current analysis, any center that recruited ≥258 patients was defined as a HRC and any center that recruited <258 patients was defined as a LRC. Traditional cardiovascular risk factors—type 2 diabetes, hypercholesterolemia, arterial hypertension, and smoking—were defined using the accepted criteria. Body mass index was calculated as a patient's weight (in kilograms) divided by the square of the patient's height (in meters), with both height and weight measured during the hospital course. Baseline and post-procedural thrombolysis in myocardial infarction blood flow were quantified according to the Thrombolysis in Myocardial Infarction group grading system.[13] The complexity of lesions was defined using the modified American College of Cardiology/American Heart Association grading system, and Class B2 and C lesions were considered as complex.[14] Left ventricular ejection fraction was calculated using the area-length method.[15] A successful PCI is defined as a residual stenosis <20% with a thrombolysis in myocardial infarction flow of 3 with no angiographic complications.[16]

The primary end point of this study was a composite of all-cause death, myocardial infarction, or stroke at 12 months after randomization. The secondary end point was major bleeding defined as types 3 to 5 bleeding according to the Bleeding Academic Research Consortium (BARC) criteria.[17] Myocardial infarction was defined according to the Third Universal Definition of Myocardial Infarction criteria.[18] Stroke was defined as the new onset of focal or global neurological deficit caused by ischemia or hemorrhage within or around the brain lasting for >24 hours or leading to death. The diagnosis of stroke required confirmation by imaging tests or an autopsy.

Follow-up was scheduled at 1 month, 6 months, and 1 year. In case of potential end point–related adverse events, source data were solicited. All serious adverse events, including the outcomes analyzed in this study, were monitored on site. Patients were monitored either via hospital visits or outpatient visits or through telephone and structured follow-up letters.

Statistical Analysis

Continuous data are presented as mean±SD or median (25th–75th percentiles) and compared using the Student *t* test or Wilcoxon rank-sum test when appropriate. Categorical variables are presented as count and proportion (percentages) and compared using the chi-squared test. The incidence of all outcomes was computed using the Kaplan–Meier method. The primary end point and mortality were shown as cumulative incidence. Other outcomes (bleeding, myocardial infarction, stroke, and stent thrombosis) were shown as cumulative incidences after accounting for competing risk. The association between the category of recruitment center (LRC versus HRC) and mortality was adjusted for potential confounders using the multivariable Cox proportional hazards model. All baseline variables that differed between LRC and HRC with a *P* value <0.1 plus the interaction term between recruitment center category and randomly assigned treatment were entered into the model. The primary outcome and stent thrombosis were analyzed in the intention-to-treat population (including all patients according to the randomly assigned trial group, irrespective of the actual treatment received). Bleeding in patient groups according to the center (ie, LRC and HRC categories) was analyzed in the intention-to-treat population. Bleeding according to study drug (ticagrelor or prasugrel) was analyzed in the modified intention-to-treat population (including all patients who received at least 1 dose of the randomly assigned study drug who were assessed for bleeding up to 7 days after study drug discontinuation). The risk estimates (hazard ratio [HR] with 95% CI) were calculated using the Cox proportional hazard model adjusting for the study drug, participating center, and stratification according to the clinical presentation. The statistical analysis was performed using the R 3.6.0 statistical package (R Foundation for Statistical Computing, Vienna, Austria). A 2-sided $P<0.05$ was considered to indicate statistical significance.

RESULTS

Baseline Data

Of the 4018 patients enrolled in 23 participating centers, 3011 patients (75%) were recruited in HRCs (7 centers recruiting 258 to 628 patients; median, 413 patients). The remaining 1007 patients (25%) were recruited in LRCs (16 centers recruiting 5 to 201 patients; median, 52 patients). The recruitment period lasted 4.5 years (from September 2013 until February 2018). As a center volume, we used the provided number of patients with ACS undergoing PCI during the feasibility check inquiries normalized for the period in which the centers enrolled patients in the study. The center volume ranged between 81 and 6000 patients. Baseline demographical and clinical data are shown in Table 1. Patients enrolled in the LRCs were slightly younger, had hypercholesterolemia less often, and had higher proportions of patients with prior PCI or prior coronary artery bypass surgery and cardiogenic shock compared with patients enrolled in the HRCs.

Table 1. Baseline Characteristics

Characteristic	Low recruitment center (n=1007)	High recruitment center (n=3011)	*P* value
Study drug			0.841
Ticagrelor	501 (49.8)	1511 (50.2)	
Prasugrel	506 (50.2)	1500 (49.8)	
Age, y	63.0±11.9	64.8±12.1	0.050
Women	225 (22.3)	731 (24.3)	0.228
Diabetes	210 (20.9)	560/3009 (22.7)	0.249
On insulin therapy	66 (7.5)	214/3009 (7.1)	0.596
Current smoker	340/997 (34.1)	1009/3004 (33.6)	0.854
Arterial hypertension	704/1006 (70.0)	2112/3005 (70.3)	0.887
Hypercholesterolemia	528/1005 (52.5)	1605/3005 (60.3)	<0.001
Prior myocardial infarction	154 (14.4)	486/3008 (16.2)	0.202
Prior percutaneous coronary intervention	200 (19.9)	716/3008 (23.8)	0.011
Prior aortocoronary bypass surgery	47 (4.7)	198/3009 (6.6)	0.034
Cardiogenic shock	8 (0.8)	57 (1.9)	0.025
Systolic blood pressure, mm Hg	144±25.4	143±24.5	0.157
Diastolic blood pressure, mm Hg	83.4±14.6	81.4±14.0	<0.001
Heart rate, beats/min	77±16	76±16	0.327
Body mass index, kg/m^2	27.8±4.6	27.8±4.5	0.727
Creatinine, μmol/L	86.2±30.5	88.5±28.4	0.031
Diagnosis on admission			<0.001
ST-segment–elevation myocardial infarction	453 (45.0)	1200 (40.0)	
Non–ST-segment–elevation myocardial infarction	495 (49.2)	1360 (45.0)	
Unstable angina	59 (5.8)	451 (15.0)	
Coronary angiography	1006 (99.9)	2998 (99.6)	0.212
Treatment strategy			<0.001
Percutaneous coronary intervention	903/1006 (89.8)	2474/3007 (82.3)	
Coronary artery bypass grafting	25/1006 (2.4)	58/3007 (1.9)	
Conservative	78/1006 (7.8)	475/3007 (15.8)	

Data are mean±SD or number (percentage). Completeness of continuous data: Systolic blood pressure was not available in 3 patients (1 in the low recruitment center patients and 2 in the high recruitment center); diastolic blood pressure was not available in 16 patients (2 in the low recruitment center and 14 in the high recruitment center); heart rate was not available in 2 patients (2 in the low recruitment center); body mass index was not available in 31 patients (2 in the low recruitment center and 29 in the high recruitment center); creatinine level was not available in 6 patients (2 in the low recruitment center and 4 in the high recruitment center). The remaining continuous data are complete.

In addition, patients recruited in the LRCs had higher diastolic blood pressure (on average), lower levels of serum creatinine, were admitted more often with ST-segment–elevation myocardial infarction or non–ST-segment–elevation myocardial infarction and less often with unstable angina, and were more likely to undergo PCI and less often coronary artery bypass surgery than patients recruited in the HRCs.

Angiographic and procedural data are shown in Table S1 and Table S2. Patients recruited in the LRCs had 3-vessel disease less often compared with patients recruited in the HRCs. Patients recruited in the LRCs had significantly higher left ventricular ejection fraction than patients recruited in the HRCs. In addition, patients recruited in the LRCs compared with those recruited in the HRCs appear to differ with respect to number of lesions treated, frequency of complex lesions, baseline thrombolysis in myocardial infarction flow grade, frequency of use of drug-eluting stents or bioresorbable vascular scaffolds, maximal stent diameter, and periprocedural pharmacological therapy (Table S2). A higher proportion of patients was discharged on aspirin and study drugs (ticagrelor and prasugrel) in the LRCs compared with the HRCs (Table S3). Drug discontinuation rate was significantly lower among patients recruited in the LRCs (101 patients; 11.6%) compared with patients recruited in the HRCs (341 patients; 14.6%) centers (*P*=0.028). Antithrombotic medication after discontinuation of study drug appears to differ little

among patients recruited in LRCs or HRCs (Table S4). Reasons for discontinuation of the study drug are shown in Table S5.

Clinical Outcome in LRCs and HRCs

The follow-up was incomplete in 31 patients (3.1%) recruited in the LRCs and 59 patients (2.0%) recruited in the HRCs (*P*=0.038). However, there was no significant difference in the proportion of patients with incomplete follow-up between the ticagrelor and prasugrel groups both in the LRC (*P*=0.377) and HRC categories (*P*=0.672). Clinical outcomes in LRCs and HRCs are shown in Table 2. The primary end point (death, myocardial infarction, or stroke) occurred in 72 patients in the LRCs and 249 patients in the HRCs (cumulative incidence, 7.3% and 8.4%, respectively; HR, 0.86; 95% CI, 0.66–1.12; *P*=0.267). Time-to-event curves for primary end point are shown in the Figure. All-cause mortality was lower among patients recruited in the LRCs (n=29) than among patients recruited in the HRCs (n=134; cumulative incidence, 2.9% versus 4.5%; HR, 0.64; 95% CI, 0.43–0.96; *P*=0.031). After adjustment in the multivariable Cox proportional hazards model (see the Methods section for variables we adjusted for), the association between recruitment in a LRC and mortality was attenuated (adjusted HR, 0.67; 95% CI, 0.44–1.00; *P*=0.052). There was no significant difference with respect to the occurrence of BARC types 3 to 5 of bleeding (secondary end point). The frequencies of BARC 1 to 2 types of bleeding or BARC types 1 to 5 of bleeding (all bleeding events) were significantly lower among patients recruited in the LRCs compared with patients recruited in the HRCs (Table 2).

To address an eventual impact of the arbitrary selection of the cutoff used to dichotomize centers in low and high recruitment categories and the center volume of patients with ACS undergoing PCI on the association between recruitment volume and mortality, we performed a sensitivity analysis by inclusion of the number of patients enrolled in each center (as a continuous variable instead of the LRC and HRC categories) and the center volume in the multivariable Cox proportional hazard model. The model showed that the recruitment number was independently associated with the risk for 1-year mortality (HR, 0.88; 95% CI, 0.80–0.97; *P*=0.011 for 100-patient decrement). The center volume was not independently associated with the risk for 1-year mortality (*P*=0.202) in this model.

Clinical Outcome According to Study Drug in LRCs and HRCs

Clinical outcome at 12 months according to study drug is shown in Table 3. Notably, there was no significant interaction between the treatment effect of ticagrelor versus prasugrel and patient recruitment category (LRC, HRC) regarding the primary efficacy end point (Figure S1) and the safety end point (Figure S2). The only significant interaction for the individual components of the primary end point was observed for mortality (*P*=0.032). All-cause mortality was significantly higher among patients assigned to ticagrelor compared with patients assigned to prasugrel in the LRCs.

DISCUSSION

The main findings of this study can be summarized as follows: (1) patients with ACS recruited in the LRCs appeared to have more favorable cardiovascular risk profiles than patients recruited in the HRCs; (2) consistent with the more favorable cardiovascular risk profiles, patients recruited in the LRCs had lower 1-year mortality and bleeding (numerically lower major bleeding

Table 2. Clinical Outcome in the Low Recruitment and High Recruitment Centers

Outcome	Low recruitment center (n=1007)	High recruitment center (n=3011)	Hazard Ratio (95% CI)	*P* value
Primary end point (death, MI, or stroke)	72 (7.3)	249 (8.4)	0.86 (0.66–1.12)	0.267
All-cause death	29 (2.9)	134 (4.5)	0.64 (0.43–0.96)	0.031
MI	39 (3.9)	117 (3.9)	1.01 (0.70–1.45)	0.966
Stroke	13 (1.3)	28 (0.9)	1.38 (0.37–1.40)	0.334
Probable or definite stent thrombosis	13 (1.3)	33 (1.1)	1.17 (0.45–1.62)	0.624
Definite stent thrombosis	10 (1.0)	24 (0.8)	1.24 (0.39–1.68)	0.564
Bleeding (BARC types 3 to 5)*	47 (4.7)	179 (6.0)	0.78 (0.57–1.08)	0.135
Bleeding (BARC types 1 to 2)	120 (12.0)	453 (15.2)	0.77 (0.63–0.95)	0.013
Bleeding (BARC types 1 to 5)	167 (16.7)	632 (21.2)	0.75 (0.62–0.90)	0.002

Data are number of events with Kaplan-Meier estimates (percentage) for primary end point and death or cumulative incidence (percentage) after accounting for competing risk for the remaining end points.

BARC indicates Bleeding Academic Research Consortium; and MI, myocardial infarction.

*Bleeding events were analyzed in the intention-to-treat population.

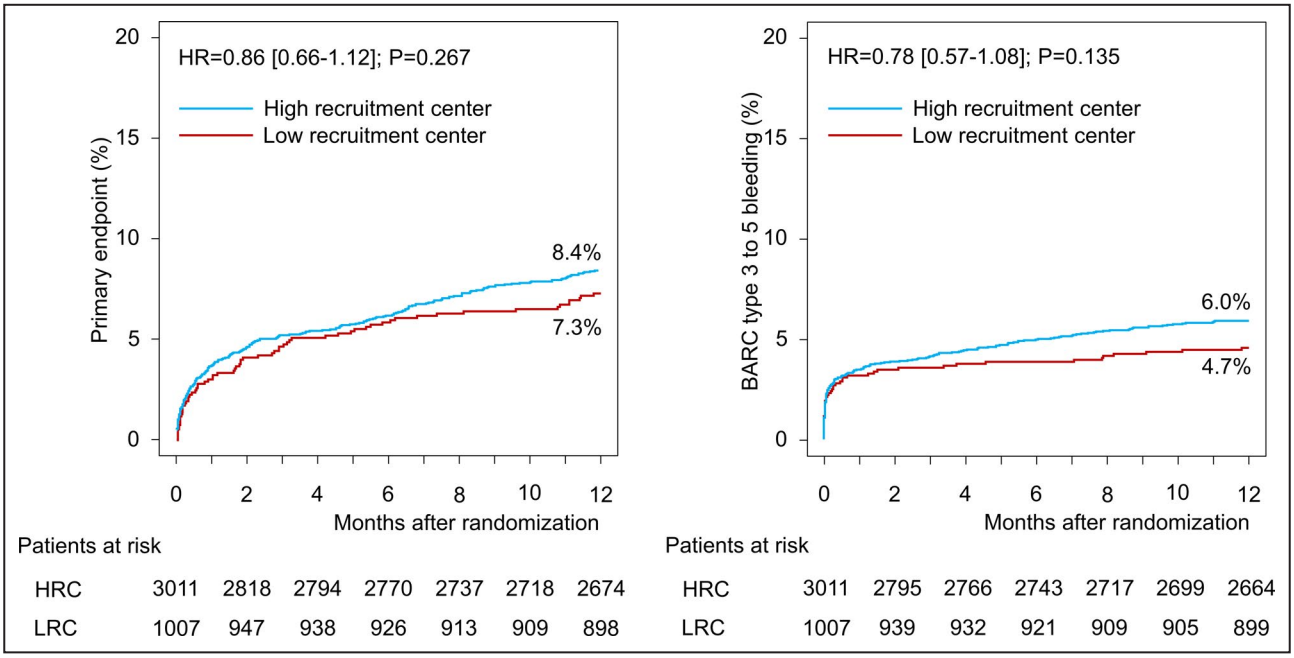

Figure. Clinical outcomes according to recruitment center volume
Left, Primary end point (composite of all-cause death, myocardial infarction, or stroke). **Right**, secondary end point of bleeding. BARC indicates Bleeding Academic Research Consortium; HR, hazard ratio; HRC, high recruitment center; and LRC, low recruitment center.

and significantly lower minor bleeding) compared with patients enrolled in the HRCs; (3) recruitment volume did not impact the treatment effect of ticagrelor versus prasugrel regarding the primary efficacy end point and the safety bleeding end point.

To the best of our knowledge, only 1 post hoc analysis by Takahashi et al.[19] from the GLOBAL LEADERS (A Clinical Study Comparing Two Forms of Anti-platelet Therapy After Stent Implantation) trial assessed the impact of recruitment and retention of the patients in the trial on all-cause mortality. The trial included 7.86% of patients treated with PCI during the recruitment period. In this study, patients recruited in the LRCs (recruitment rate below the median value) and those who consented withdrawal had significantly higher 2-year mortality compared with patients from the HRCs or those with complete follow-up, respectively. In both cases, the significance for the association with mortality was attenuated after an adjustment for baseline data. Of note, patients enrolled in the LRCs had more favorable cardiovascular risk profiles than patients enrolled in the HRCs. Our study also found that patients enrolled in the LRCs had a more favorable cardiovascular risk profile and lower mortality compared with patients enrolled in the HRC. Although there were differences between our study and the analysis from the GLOBAL LEADERS trial with respect to the individual characteristics, both studies evidenced a better cardiovascular risk profile of patients recruited in the LRCs compared with patients recruited in the HRCs. It has been estimated that 84% to 98% of screened patients ultimately were not recruited in the RCT,[20] raising concerns regarding the representativeness of patients recruited in the RCT in relation to patients encountered in daily clinical practice.[21] Our study and the study by Takahashi et al.[19] suggest that the representativeness of patients recruited in a RCT may be further worsened by recruitment in the LRCs. The most common reasons for noninclusion of the patients in the GLOBAL LEADERS trial were travel/expense burden for patients, exclusion criteria such as need for oral anticoagulant drugs, and participation of the investigator in competing PCI trials.[19] Furthermore, a center with a low record of successful performance in prior trials or with little focus on clinical trials and low investigator enthusiasm may increase the likelihood of failure to meet recruitment targets.[22] The reasons why patients with better cardiovascular risk profiles are more likely to be recruited in a LRC remains unclear. However, hypothetically they may include limited knowledge of the study protocol, unwillingness on the side of investigators to apply drugs/devices of unproven efficacy or safety in patients who were at high risk and sicker or issues related to the center's prestige if a poor outcome was perceived as more probable in patients who were high risk. Nevertheless, recruitment of patients with more benign cardiovascular risks in the LRCs may explain the lower incidence of overall bleeding, drug discontinuation, and mortality in the LRCs versus HRCs, as shown in the current study.

Table 3. Clinical Outcome According to Study Drug in the Low Recruitment and High Recruitment Centers

Outcome	Low recruitment center (n=1007)		Hazard ratio (95% CI)	*P* value	High recruitment center (n=3011)		Hazard ratio (95% CI)	*P* value	*P* value for interaction
	Ticagrelor (n=501)	Prasugrel (n=506)			Ticagrelor (n=1511)	Prasugrel (n=1500)			
Primary outcome (death, myocardial infarction, or stroke)	42 (8.5)	30 (6.0)	1.42 (0.89–2.28)	0.137	142 (9.5)	107 (7.2)	1.33 (1.04 –1.72)	0.025	0.800
All-cause death	21 (4.2)	8 (1.6)	2.67 (1.18–6.02)	0.018	69 (4.6)	65 (4.4)	1.05 (0.75–1.48)	0.761	0.032
Myocardial infarction	20 (4.0)	19 (3.8)	1.07 (0.57–2.01)	0.827	76 (5.1)	41 (2.8)	1.86 (1.27–2.72)	0.001	0.141
Stroke	7 (1.4)	6 (1.2)	1.18 (0.40–3.52)	0.762	15 (1.0)	13 (0.9)	1.14 (0.54–2.41)	0.720	0.961
Definite and probable stent thrombosis	5 (1.0)	8 (1.6)	0.63 (0.21–1.93)	0.421	21 (1.4)	12 (0.8)	1.74 (0.86–3.54)	0.125	0.127
Definite stent thrombosis	4 (0.8)	6 (1.2)	0.67 (0.19–2.39)	0.542	18 (1.2)	6 (0.4)	2.99 (1.18–7.53)	0.020	0.057
Safety end point (BARC types 3 to 5 bleeding)*	21 (4.6)	18 (4.0)	1.15 (0.61–2.15)	0.672	74 (6.0)	62 (5.2)	1.15 (0.82–1.61)	0.423	0.955
Safety end point (BARC types 2 to 5 bleeding)	46 (10.4)	43 (9.7)	1.06 (0.70–1.60)	0.795	141 (11.4)	125 (10.5)	1.10 (0.86–1.40)	0.447	0.875
Safety end point (BARC types 1 to 5 bleeding)	81 (18.3)	72 (16.3)	1.11 (0.81–1.53)	0.508	266 (21.7)	293 (24.4)	0.88 (0.74–1.04)	0.128	0.196

Data are number of events with Kaplan-Meier estimates (percentage) for primary end point and death or cumulative incidence (percentage) after accounting for competing risk for the remaining end points. BARC indicates Bleeding Academic Research Consortium.
*Bleeding events were analyzed in the modified intention-to-treat population.

We did not find a significant difference with respect to the primary or secondary end points according to the recruitment in a LRC or HRC. The exact reasons why differences in baseline cardiovascular risk and other differences (completeness of follow-up or drug discontinuation rate) in patients recruited in a LRC or HRC did not impact on the main study outcomes remain unknown. However, central event adjudication may have attenuated at least partially the center-related differences. The finding that patients recruited in the LRCs have lower mortality compared with patients recruited in the HRCs is in line with the findings of the GLOBAL LEADERS trial.[19] The reasons why patients recruited in the LRCs showed lower mortality compared with patients enrolled in the HRCs are not entirely clear. However, some putative explanations may be offered. First, as shown in our study and the GLOBAL LEADERS trial,[19] patients recruited in the LRCs had significantly more benign cardiovascular risk profiles. The evidence available strongly suggests that baseline cardiovascular risk is 1 of the most important correlates of the subsequent prognosis in patients with ACS.[23] Second, patients recruited in the LRCs had more often incomplete follow-ups. Because the vital status of patients lost to follow-up was unknown, it is likely that some of them may have already died, increasing the likelihood of underreported mortality among patients recruited in the LRCs. Third, a higher proportion of patients recruited in the LRCs were discharged on the study drugs (ticagrelor and prasugrel) compared with patients recruited in the HRCs. The difference in drug therapy at discharge may reflect higher proportions of patients undergoing PCI and patients with ACS diagnoses at discharge among the patients enrolled in the LRCs compared with the patients enrolled in the HRCs. Nevertheless, an impact of the drug therapy differences at discharge on prognosis cannot be refuted. Fourth, patients enrolled in the LRCs had significantly lower rates of study drug discontinuation. Discontinuation of evidence-based medications after myocardial infarction has been shown to be associated with increased subsequent mortality.[24] Fifth, patients enrolled in LRCs had lower incidences of bleeding. Although the association with mortality is strongest for major bleeding, even minor bleeding (BARC type 2 bleeding) is associated with a significant increase in the risk for mortality.[25,26]

An important finding of this study is that, despite differences in risk profile of the patients enrolled in LRCs versus HRCs, there was no significant interaction between the treatment effect of ticagrelor versus prasugrel and patient recruitment category (LRC, HRC) regarding the primary efficacy and safety end point. Thus, the low recruitment volume in 70% of the participating centers did not impact the main treatment effect observed in the entire population of

the ISAR-REACT 5 trial. However, all-cause mortality was significantly higher among patients assigned to ticagrelor compared with patients assigned to prasugrel in the LRCs. We have no clear explanation for the significant study drug–recruitment center interaction regarding mortality. However, it may be a play of chance favored by the limited number of deaths in the LRC group and multiple comparisons performed in the present study.

The current analysis has limitations. First, the definition of LRC versus HRC based on the upper 30% of the centers with the highest number of recruited patients is arbitrary. However, the association between recruitment volume and the risk for mortality was even stronger with the use of the actual number of enrolled patients instead of LRC and HRC categories. Second, the numbers of events were small, particularly in the group of patients enrolled in the LRCs. Thus, a possibility that some of the findings are a play of chance further amplified by multiple testing cannot be refuted. For these reasons, the current findings may be seen as exploratory or hypothesis generating.

In conclusion, patients with ACS recruited in the LRCs appear to have more favorable cardiovascular risk profiles and lower 1-year mortality rates compared with patients recruited in the HRCs. Recruitment volume did not affect the treatment effect of ticagrelor versus prasugrel regarding the primary efficacy end point and the safety bleeding end point.

ARTICLE INFORMATION

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Supplementary Material

Tables S1-S5
Figure S1-S2.

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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

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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
Planed 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

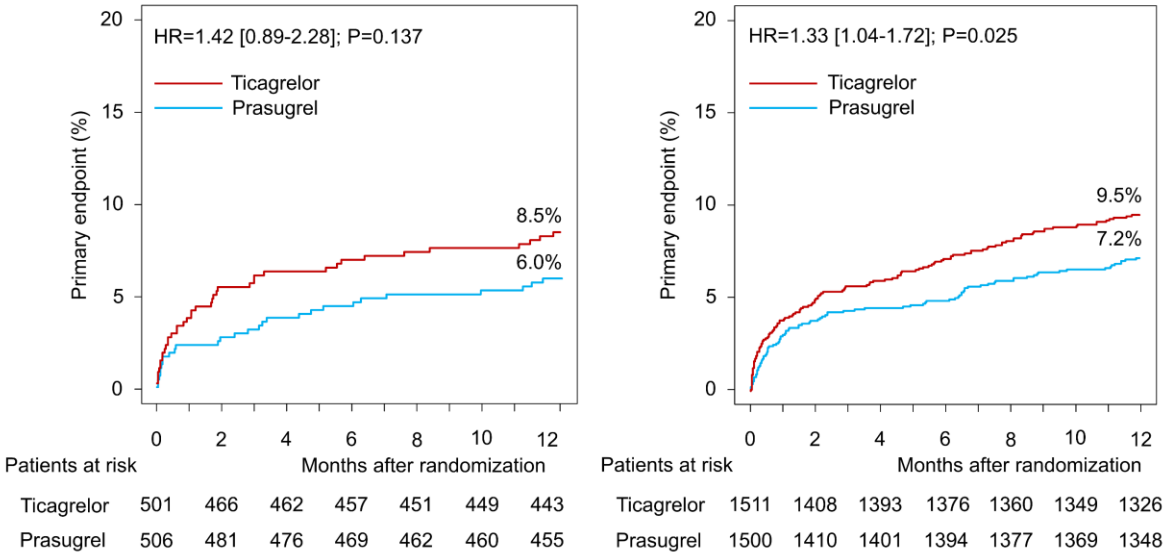

Figure S1. Primary endpoint (composite of all-cause death, myocardial infarction or stroke) in patients assigned to ticagrelor or prasugrel in low recruitment centers (left panel) and high recruitment centers (right panel).

HR=hazard ratio

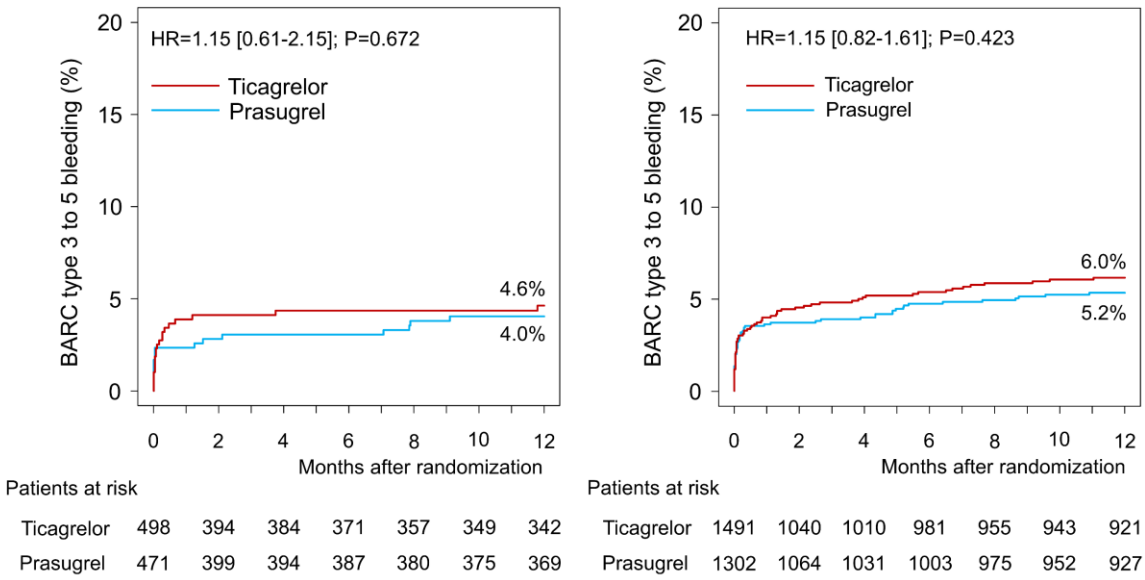

Figure S2. Secondary endpoint of bleeding in patients assigned to ticagrelor or prasugrel in low recruitment centers (left panel) and high recruitment centers (right panel).

BARC= Bleeding Academic Research Consortium; HR=hazard ratio