Circulation

ORIGINAL RESEARCH ARTICLE

Comparison of Reduced-Dose Prasugrel and Standard-Dose Clopidogrel in Elderly Patients With Acute Coronary Syndromes Undergoing Early Percutaneous Revascularization

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BACKGROUND: Elderly patients are at elevated risk of both ischemic and bleeding complications after an acute coronary syndrome and display higher on-clopidogrel platelet reactivity compared with younger patients. Prasugrel 5 mg provides more predictable platelet inhibition compared with clopidogrel in the elderly, suggesting the possibility of reducing ischemic events without increasing bleeding.

METHODS: In a multicenter, randomized, open-label, blinded end point trial, we compared a once-daily maintenance dose of prasugrel 5 mg with the standard clopidogrel 75 mg in patients >74 years of age with acute coronary syndrome undergoing percutaneous coronary intervention. The primary end point was the composite of mortality, myocardial infarction, disabling stroke, and rehospitalization for cardiovascular causes or bleeding within 1 year. The study was designed to demonstrate superiority of prasugrel 5 mg over clopidogrel 75 mg.

RESULTS: Enrollment was interrupted, according to prespecified criteria, after a planned interim analysis, when 1443 patients (40% women; mean age, 80 years) had been enrolled with a median follow-up of 12 months, because of futility for efficacy. The primary end point occurred in 121 patients (17%) with prasugrel and 121 (16.6%) with clopidogrel (hazard ratio, 1.007; 95% confidence interval, 0.78–1.30; P=0.955). Definite/probable stent thrombosis rates were 0.7% with prasugrel versus 1.9% with clopidogrel (odds ratio, 0.36; 95% confidence interval, 0.13–1.00; P=0.06). Bleeding Academic Research Consortium types 2 and greater rates were 4.1% with prasugrel versus 2.7% with clopidogrel (odds ratio, 1.52; 95% confidence interval, 0.85–3.16; P=0.18).

CONCLUSIONS: The present study in elderly patients with acute coronary syndromes showed no difference in the primary end point between reduced-dose prasugrel and standard-dose clopidogrel. However, the study should be interpreted in light of the premature termination of the trial.

CLINICAL TRIAL REGISTRATION: URL: https://www.clinicaltrials.gov. Unique identifier: NCT01777503.

Clinical Perspective

What Is New?

- Dual antiplatelet therapy, the standard of care after an acute coronary syndrome (ACS), is associated with a higher bleeding risk in the elderly.
- Compared with clopidogrel, the third-generation $P2Y_{12}$ antagonist, prasugrel, at the standard 10-mg dose, has reduced ischemic events in patients with ACS undergoing percutaneous coronary intervention at the cost of increased bleeding, particularly in patients ≥75 years of age.
- On the basis of pharmacodynamic data, a 5-mg dose has been recommended for use in elderly patients, but no clinical data are available.
- The results of the Elderly ACS 2 study could not show overall clinical benefit of prasugrel 5 mg versus clopidogrel in elderly patients with ACS undergoing early percutaneous coronary intervention.

What Are the Clinical Implications?

- Elderly patients with ACS treated by percutaneous coronary intervention via the radial approach and with systematic use of proton pump inhibitors show low rates of ischemic and bleeding events.
- Fine-tuning of $P2Y_{12}$ blockade either by using more consistent platelet inhibition (as in the present study) or by adjusting the dose with platelet function testing (as in the ANTARCTIC study [Tailored Antiplatelet Therapy Versus Recommended Dose of Prasugrel]) is not likely to improve outcome compared with the standard combination of aspirin and clopidogrel.
- Future studies should investigate whether a shorter duration of dual antiplatelet therapy in the elderly may further reduce bleeding to further improve net clinical outcomes.

Elderly patients represent about a third of the acute coronary syndromes (ACS) population,[1,2] but they have traditionally been underrepresented in clinical trials.[3,4] Only recently, specific randomized trials have been carried out in elderly patients with ACS,[5–7] showing the overall superiority of an early invasive approach over a conservative one. This conclusion also is supported by observational data showing improved outcomes of the elderly population with the progressive shift over time to an almost systematic invasive strategy.[1,2,8,9]

Antiplatelet therapy has become an essential part of ACS treatment, particularly for patients undergoing percutaneous coronary intervention (PCI),[10–13] with the combination of aspirin and the $P2Y_{12}$ receptor blocker clopidogrel being the recognized standard of care until 2 more powerful drugs, prasugrel and ticagrelor, showed superiority with regard to ischemic end points in large randomized trials.[14,15] However, the bleeding hazard associated with intense platelet inhibition is particularly important in elderly patients treated invasively, rendering questionable the benefit-to-risk ratio of powerful antiplatelet agents in these patients.[14,16] Indeed, according to recent registries, clopidogrel remains the most widely used $P2Y_{12}$ receptor inhibitor in the elderly ACS population.[17]

With regard to prasugrel, the 5-mg dose has been recommended for selected patients ≥75 years of age on the basis of pharmacokinetic data,[18] but this low dose has never been tested in elderly patients with ACS treated with PCI. There is therefore a strong rationale to prove the efficacy and safety of this dose of prasugrel in an old ACS population treated invasively. In platelet function studies, elderly patients have frequently shown high platelet reactivity while on clopidogrel,[19] and the switch of resistant cases to prasugrel 5 mg has been found to provide effective platelet inhibition.[20] A long-term platelet function study has also shown a persistent, more predictable, and slightly more powerful effect of prasugrel 5 mg versus clopidogrel in elderly patients with non–ST-elevation (NSTE)–ACS treated conservatively, without a difference in bleeding but with neutral effect on ischemic end points.[21,22] With the present randomized Elderly ACS 2 study, we aimed at comparing prasugrel 5 mg with clopidogrel 75 mg maintenance dose, in addition to aspirin, in elderly patients with ACS undergoing early PCI.

METHODS

The data, analytical methods, and study materials will be made available on request to other researchers for purposes of reproducing the results or replicating the procedure. The Elderly ACS 2 trial is a randomized, open-label, blinded end point trial carried out at 32 centers in Italy. We enrolled patients >74 years of age with ST-segment–elevation (STE)— or NSTE-ACS treated with PCI during index admission. To be eligible, patients with NSTE-ACS had to show at least 1 of the following characteristics: elevated troponin levels, diabetes mellitus, prior myocardial infarction (MI), ≥1 new ischemic episode while on standard treatment during the index hospitalization, or stent thrombosis. We excluded patients with a history of stroke, gastrointestinal or genitourinary bleeding of clinical significance within the previous 6 weeks, hemoglobin level on admission <10 g/dL unless this was considered to be secondary to renal dysfunction or known myelodysplasia, platelet count <90 000 cells/mL, secondary causes of ischemia, ongoing oral anticoagulant treatment or a spontaneous international normalized ratio >1.5 at the time of screening, concomitant severe obstructive lung disease, malignancy, or neurological deficit limiting follow-up or adherence to the study protocol. Patients unable to give at least verbal informed consent to the study or already under treatment with prasugrel or ticagrelor were also excluded. The protocol was approved by the ethics committee of the coordinating center and subsequently by the ethics committees of all the participating centers and has previously been published.[23] The study was done in accordance with the Declaration of

Helsinki and following the Good Clinical Practice Guidelines. All patients provided written informed consent.

Participants were randomly assigned to either clopidogrel (300–600 mg loading dose [at investigator discretion] followed by 75 mg once daily) or prasugrel (60 mg loading dose followed by 5 mg once daily) with a 1:1 allocation using an electronic case report form–based randomization (Mediolanum Cardio Research, Milan, Italy). Treatment assignment was stratified by center and type of ACS (STE versus NSTE) according to a complete permutated blocks scheme. Study investigators and patients were not masked to treatment allocation, but allocation was concealed to an independent event adjudication committee responsible for end point adjudication.

In patients with STEMI undergoing primary PCI, the drugs could be given as soon as possible after the diagnosis, yet the first administration of the study drug could also take place after angiography or soon after PCI (eg, on arrival in the coronary care unit), particularly in patients treated during PCI with glycoprotein IIb/IIIa receptor blockers. For patients treated with bivalirudin monotherapy during PCI, it was strongly recommended that the loading dose of the investigational drugs be administered before PCI. In patients with NSTE-ACS, randomization was to take place after angiography, and the loading dose should be administered either immediately before PCI or on arrival in the coronary care unit. Ongoing clopidogrel treatment, either preexisting or started as soon as the diagnosis of NSTE-ACS was made (with a loading dose of 300 or 600 mg left to the investigators' discretion), did not preclude enrollment. In this case, patients randomized to clopidogrel were to continue clopidogrel 75 mg daily without a further loading dose; those randomized to prasugrel received a 30 mg loading dose immediately after randomization.

All patients were to receive 325 mg aspirin on admission and then 75 to 100 mg daily throughout follow-up. Proton pump inhibitors were recommended in all patients throughout the study. The selection of periprocedural anticoagulants and glycoprotein IIb/IIIa receptor blockers was left to the investigators' discretion. Whereas the use of oral anticoagulants at the time of the index event was a contraindication to enrollment

in the study, their subsequent use for conditions that could have developed during follow-up (eg, atrial fibrillation) was left to the discretion of the attending physician as clinically indicated. For safety reasons, patients in the prasugrel treatment arm with an acute ischemic cerebrovascular event after the initiation of study treatment had to discontinue prasugrel, yet they remained in the study until the end of follow-up. Follow-up visits were to take place at 30 days, 6 months, and 12 months after randomization. All enrolled patients who had not completed the 12-month follow-up period at the time of trial interruption were to be followed up until the last enrolled patient had completed at least 3 months of follow-up.

As in the previous Italian Elderly ACS study,[6] the primary end point was the composite of all-cause mortality, MI, disabling stroke, and rehospitalization for cardiovascular causes or bleeding within 1 year. All definitions of the primary end point components have been published previously.[23] The secondary end points include the global occurrence of cardiovascular death, MI, and stroke; all-cause mortality, cardiovascular mortality at 1 year, and MI at 1 year; Bleeding Academic Research Consortium[24] type 2 or 3 bleeding within 12 months (for bleeding occurring during index or subsequent hospitalizations); any stroke within 12 months; and total number of days spent in hospital within 12 months after index admission. Probable and definite stent thrombosis events were adjudicated according to the Academic Research Consortium criteria.[25] All the events were adjudicated by an independent Event Adjudication Committee (including 3 expert cardiologists and 1 neurologist) blinded to study group assignment. The statistical analyses, including the planned interim analysis, were carried out by investigators blinded to drug assignment.

Statistical Analysis

The sample size calculations were based on the primary end point rate at 12 months observed in the Italian Elderly ACS study[6] (which, however, had included only patients with NSTE-ACS) with a conservative estimate in the clopidogrel arm set at 25%. Under the assumptions of a clinically relevant expected risk reduction of 20% and a constant hazard ratio of 0.80, with
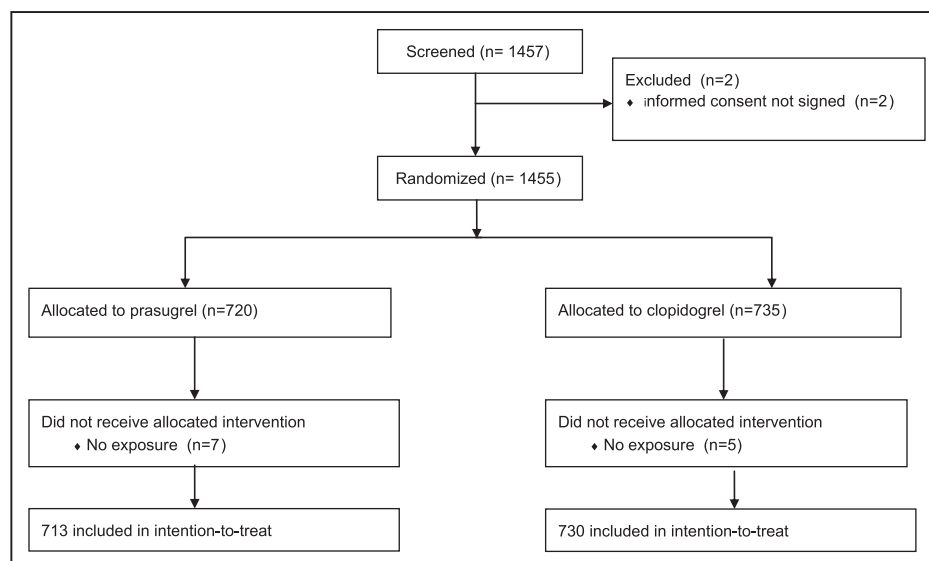

Figure 1. Trial profile.

Table 1. Baseline Clinical Characteristics

	Prasugrel (n=713)	Clopidogrel (n=730)
Age, median (interquartile range), y	80 (77–84)	80 (77–84)
Sex		
Female, n (%)	294 (41)	282 (39)
Male, n (%)	419 (59)	448 (61)
Body weight, kg (interquartile range)	72 (65–80)	72 (65–80)
Body mass index, kg/m² (interquartile range)	26 (24–28)	26 (24–28)
Medical history		
Family history of cardiovascular disease, n (%)	97 (14)	118 (16)
Diabetes mellitus, n (%)	215 (30)	204 (28)
Hypertension, n (%)	554 (78)	566 (78)
Hypercholesterolemia, n (%)	332 (47)	313 (43)
Current smoker, n (%)	62 (9)	69 (9)
Chronic respiratory failure, n (%)	43 (6)	44 (6)
Liver disease, n (%)	10 (1.4)	14 (2)
eGFR* at admission, mL/min, mean (SD)	55 (19)	57 (21)
Hemoglobin at admission, g/dL		
Men, mean (SD)	13.8 (1.6)	13.8 (1.5)
Women, mean (SD)	12.7 (1.4)	12.8 (1.5)
Neurological disorders, n (%)	20 (3)	26 (3)
Malignancies, n (%)	22 (3)	24 (3)
Previous cardiovascular events		
MI, n (%)	137 (19)	137 (19)
Percutaneous coronary interventions, n (%)	145 (20)	119 (16)
Coronary artery bypass grafting, n (%)	59 (8)	69 (10)
Peripheral vascular disease, n (%)	59 (8)	66 (9)
Atrial fibrillation, n (%)	32 (5)	24 (3)
Ongoing cardiovascular medications		
Aspirin, n (%)	366 (62)	350 (59)
Clopidogrel, n (%)	105 (18)	109 (18)
β-Blockers, n (%)	247 (42)	247 (42)
Calcium antagonists, n (%)	171 (29)	178 (30)
ACE inhibitors or ARBs, n (%)	399 (56)	391 (54)
Diuretics, n (%)	198 (34)	224 (38)
Nitrates, n (%)	107 (18)	104 (18)
Statins, n (%)	267 (45)	262 (44)

Data are number (%), mean (SD), or median (interquartile range). There are no significant differences between treatment groups.

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor antagonist; eGFR, estimated glomerular filtration rate; and MI, myocardial infarction.

*eGFR by the Cockcroft-Gault formula.

Table 2. Characteristics of Index ACS Event

	Prasugrel (n=713)	Clopidogrel (n=730)
Type of ACS		
STEMI, n (%)	298 (42)	297 (41)
NSTEMI, n (%)	344 (48)	350 (47)
Unstable angina, n (%)	71 (10)	83 (12)
Time from symptoms to PCI		
STEMI, h (SD)	4.8 (4.4)	4.8 (4.6)
NSTEMI, h (SD)	29 (17)	29 (17)
Killip class		
I, n (%)	573 (83)	601 (85)
II, n (%)	88 (12)	81 (11)
III, n (%)	26 (4)	21 (3)
IV, n (%)	5 (1)	7 (1)
Left ventricular ejection fraction, % (SD)	49 (10)	48 (10)
Coronary angiography		
Radial access, n (%)	537 (76)	572 (79)
1-Vessel disease, n (%)	289 (41)	288 (40)
2-Vessel disease, n (%)	194 (27)	229 (32)
3-Vessel disease or greater, n (%)	224 (31)	208 (29)
Left main, n (%)	56 (4)	43 (3)
TIMI flow (culprit vessel)		
0, n (%)	340 (25)	331 (24)
1, n (%)	74 (5)	86 (6)
2, n (%)	178 (13)	170 (12)
3, n (%)	789 (57)	792 (57)
PCI performed, n (%)	707 (99)	726 (99.5)
Total treated lesions, n	918	953
Treated lesions per patient, mean (SD)	1.34 (0.64)	1.35 (0.63)
Mean stents per patient, mean (SD)	1.60 (0.92)	1.61 (0.87)
Stenting	849 (93)	896 (94)
Drug-eluting balloons, n (%)	24 (3)	19 (2)
Plain balloon angioplasty, n (%)	44 (5)	37 (4)
Drug-eluting stents implanted, n (%)	630 (74)	686 (76)
Bare metal stents implanted, n (%)	151 (18)	166 (18.5)
Procedural success, n (%)	682 (97)	705 (97)

Data are number (%) or mean (SD). There are no significant differences between treatment groups.

ACS indicates acute coronary syndrome; NSTEMI, non–ST-segment–elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment–elevation myocardial infarction; and TIMI, Thrombolysis in Myocardial Infarction.

statistical significance at 2-sided α≤0.05 for a log-rank test and at least 80% power, at least 492 primary adjudicated events were needed, leading to an estimated enrollment of ≈2000 patients. An interim analysis was planned to reassess the sample size calculation on the basis of actual probability of the primary end point after the first 1000 patients had completed 1 year of follow-up.[24] This analysis, conducted in December 2016, showed a 1-year cumulative primary end point proportion of 19% (compared with the aggregate 22.5% hypothesized on study planning), with an observed between-group difference that was virtually null (hazard ratio, 1.015; 95% confidence interval [CI], 0.76–1.36). According to the protocol, because a relative risk reduction of >20% was not confirmed

Table 3. Drug Therapy During Admission and at Discharge

	Prasugrel (n=713), n (%)	Clopidogrel (n=730), n (%)
Periprocedural medications		
Aspirin	682 (96)	681 (95)
Clopidogrel before randomization	348 (49)	398 (55)
Glycoprotein IIb/IIIa antagonists	121 (17)	114 (16)
Unfractionated heparin	564 (80)	582 (81)
Low-molecular-weight heparin	137 (19)	139 (19)
Bivalirudin	54 (8)	70 (10)
Medications at discharge		
Aspirin	690 (99)	709 (99)
Proton pump inhibitors	646 (93)	661 (92)
β-Blockers	543 (78)	562 (78)
Calcium antagonists	151 (22)	114 (20)
ACE inhibitors or ARBs	578 (83)	595 (83)
Diuretics	283 (41)	276 (38)
Nitrates	87 (12)	96 (13)
Statins	662 (95)	682 (95)

There are no significant differences between treatment groups.

ACE indicates angiotensin-converting enzyme; and ARB, angiotensin receptor antagonist.

and the between-group difference resulted to be lower than forecasted, a sample size was recalculated considering a baseline primary end point rate of 0.19 and a difference of 0.01, 0.02, 0.03, 0.035, and 0.04. The sample size recalculation was carried out according to the "simple" log-rank procedure (as for the original sample size calculation) but allowing 5% loss to follow-up and specifying a 2-tailed significance level of 0.05. The detailed calculation tables are included in the interim analysis report (available on request). Briefly, for an optimistic difference of 0.02 (ie, 0.19 versus 0.17), the number of patients required should have been ≈6000 per group. In the same analysis, no safety issues were confirmed. As predefined in the protocol amendment 3,[23] on the basis of these results, the steering committee made the decision to close patient enrollment for futility on January 25, 2017. The decision was communicated to all involved investigators (by phone calls and a confidential letter), to local ethics committees, and to the Italian Medicines Agency. A common study end date (April 25, 2017) was also fixed, 3 months after the inclusion of the last patient in the study. Study unblinding took place after the last patient had completed the 3-month follow-up.

The analysis was performed in the intention-to-treat population. Cumulative no-event probability at 12 months (365 days) of the primary and secondary end points was estimated with the Kaplan-Meier method by considering the time of occurrence of the first event of the composite end point, and the hazard ratio was calculated together with its 95% CI by use of the Cox proportional hazard model. Data on patients lost to follow-up were censored at the time of last contact. A Fisher exact test was used for the between-group comparison on other end points of interest such as definite and

probable stent thrombosis and Bleeding Academic Research Consortium type 2 or greater bleeding within 12 months.

Quantitative variables are described with arithmetic mean or median as indicated, interquartile range, minimum and maximum, and SD. Absolute frequencies and percentages were used for qualitative variables. The 95% CIs are also provided. All statistical tests have been performed with 2-sided $\alpha=0.05$ and 95% CI unless otherwise specified. All analyses were performed with SAS version 9.2.

RESULTS

Between November 15, 2012, and January 25, 2017, we randomly assigned 1443 patients to clopidogrel (n=730) or prasugrel (n=713) (Figure 1). Forty percent of the patients were women, and the mean age was 80.6±4.5 years. As shown in Tables 1 and 2, the baseline clinical and angiographic characteristics were well matched between groups, as were the coronary interventional procedures. An ST-segment–elevation myocardial infarction was diagnosed in 42% of the cases, whereas 48% had non–ST-segment–elevation myocardial infarction and 10% had unstable angina. The median follow-up duration was 12.1 months (range, 3–13 months). Only 23 patients (1.46%) were lost to follow-up, with no events observed before exit from the study. Periprocedural and discharge therapies, shown in Table 3, also were well matched between the 2 groups. The vast majority of patients were treated with a radial access. Three quarters of patients in both groups had drug-eluting stents implanted, with first-generation (sirolimus, paclitaxel) drug-eluting stents rarely used (7.5% in the prasugrel group, 5.1% in the clopidogrel group). A proton pump inhibitor was prescribed in 92% of the patients at hospital discharge. At the last follow-up visit, dual antiplatelet therapy was being taken by 621 patients (87%) in the prasugrel group compared with 682 patients (93%) in the clopidogrel group. Conversely, premature treatment discontinuations were more frequent in the prasugrel group (13% versus 7%), the main reason being the occurrence of adverse events (10.8% versus 6%).

Primary and Secondary End Points

The primary end point occurred in 121 patients (17.0%) in the prasugrel group and 121 patients (16.6%) in the clopidogrel group (hazard ratio, 1.007; 95% CI, 0.78–1.30; P=0.95; Figure 2 and Table 4). None of the clinically relevant subgroups of patients showed differences in the primary end point between the randomized treatments (Figure 3). As shown in Table 4, none of the secondary end points differed significantly between the treatment arms. There were 19 cases (1.3%) of probable or definite stent thrombosis: 5 (0.7%) with prasugrel and 14 (1.9%) with clopidogrel (odds ratio,
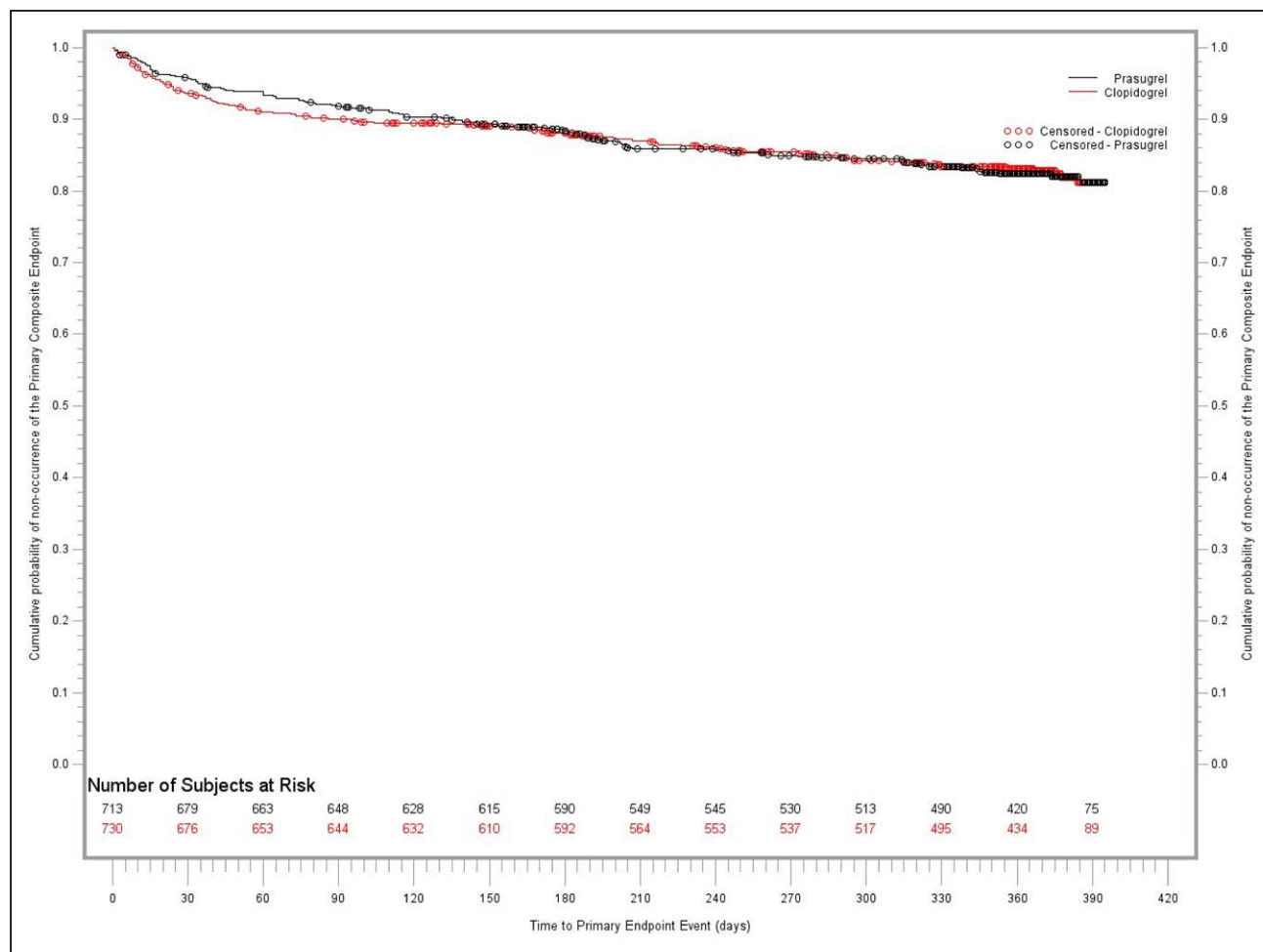
Figure 2. Kaplan-Meier estimate of the survival function for the primary composite end point of all-cause mortality, myocardial infarction, disabling stroke, and rehospitalization for cardiovascular causes or severe bleeding up to 12 months after inclusion.
Intention-to-treat population, adjudicated events.

0.36; 95% CI, 0.13–1.00; P=0.06). As shown in Table I in the online-only Data Supplement, stent thrombosis was numerically more frequent with clopidogrel in all relevant subgroups.

The overall rate of Bleeding Academic Research Consortium types 2, 3, and 5 was 4.1% with prasugrel versus 2.7% with clopidogrel (hazard ratio, 1.53; 95% CI, 0.85–3.16; P=0.18). One fatal bleeding occurred in the prasugrel group as a consequence of an accidental fall causing subarachnoid hemorrhage. Twelve red blood cell units were transfused in 12 patients in the prasugrel group (1.7%) and 9 in 9 patients in the clopidogrel group (1.2%).

DISCUSSION

In this large randomized trial of elderly patients with ACS undergoing PCI during the index admission, we observed similar rates of major cardiovascular events in the group assigned to prasugrel 5 mg maintenance dose compared with the standard treatment with clopidogrel 75 mg. This result applies also to patient subgroups that had shown particular benefit from prasugrel 10 mg in the TRITON-TIMI 38 study (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis in Myocardial Infarction 38), such as those with diabetes mellitus and those with ST-segment–elevation myocardial infarction.[14]

These data need to be interpreted in light of the pharmacodynamic data that were accruing while our trial was ongoing. The TRILOGY-ACS (Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes) platelet function substudy of patients with NSTE-ACS treated conservatively[21] and the GENERATIONS trial (Comparison of Prasugrel and Clopidogrel in Very Elderly and Non-Elderly Patients With Stable Coronary Artery Disease) in patients with stable coronary disease[26] showed that, although prasugrel 5 mg induced a significantly higher

Table 4. End Points up to 12-Month Follow-Up

	Prasugrel (n=713)	Clopidogrel (n=730)	HR (95% CI)	P Value
Primary end point*, n (%)	121 (17.0)	121 (16.6)	1.01 (0.78–1.30)	0.96
All-cause death†, n (%)	36 (5.0)	28 (3.8)		
MI†, n (%)	14 (2.0)	19 (2.6)		
Disabling stroke†	1 (0.1)	6 (0.8)		
Rehospitalization for cardiovascular causes†	55 (7.7)	57 (7.8)		
Rehospitalization for bleeding†	15 (2.1)	11 (1.5)		
Key secondary end points: all-cause death and MI, n (%)	60 (8.4)	60 (8.2)	1.02 (0.71–1.45)	0.93
Cardiovascular death, n (%)	26 (3.6)	31 (4.2)	0.85 (0.51–1.4)	0.55
Strokes, n (%)	7 (1.0)	13 (1.8)	0.55 (0.22–1.37)	0.20
Definite/probable stent thrombosis, n (%)	5 (0.7)	14 (1.9)	0.36 (0.13–1.00)‡	0.06§
Acute, n	1	1		
Subacute, n	4	12		
Late, n	—	1		
Bleeding leading to new hospitalization BARC 2, n (%)	8 (1.1)	7 (0.9)		
BARC 3, n (%)	9 (1.2)	9 (1.2)		
BARC 2, 3, n (%)	17 (2.3)	16 (2.1)		
All bleedings BARC 2, n (%)	16 (2.2)	8 (1.1)	1.52 (0.85–3.16)‡	0.18§
BARC 3, n (%)	12 (1.6)	12 (1.6)		
BARC 5, n (%)	1 (0.1)	0		
BARC 2, 3, 5, n (%)	29 (4.1)	20 (2.7)		

BARC indicates Bleeding Academic Research Consortium; CI, confidence interval; HR, hazard ratio; and MI, myocardial infarction.

*Primary end point: composite of all-cause death, MI, disabling stroke, rehospitalization for cardiovascular causes, and rehospitalization for bleeding.

†Only first event.

‡Odds ratio and 95% CI.

§Fisher exact test (2-sided).

level of platelet inhibition compared with clopidogrel 75 mg, the absolute difference in maximum platelet aggregation values between groups was small. Thus, the lack of significant difference in clinical outcomes maybe attributable, at least in part, to a rather small difference in the level of platelet inhibition. The more sophisticated approach used in the ANTARCTIC study (Tailored Antiplatelet Therapy Versus Recommended Dose of Prasugrel) of adjusting the selection and the dosage of the $P2Y_{12}$ receptor blocker according to the results of platelet inhibition testing has also failed to improve ischemic or safety outcomes in elderly patients treated with coronary stenting for ACS.[27]

A second hypothesis might be that with the improvement in stent technology and operator expertise, compared with the era when prasugrel showed superiority over clopidogrel in the TRITON-TIMI 38 study,[14] the added value of a more predictable response to $P2Y_{12}$ receptor blockade is lower. Considering the advanced age of the patient population, on average 19 years older than that of the PCI CURE study (*PCI*-Clopidogrel in Unstable Angina to Prevent Recurrent Events)[28] and 21 years older than that of the TRITON study,[14] overall

ischemic events were lower than expected in the present study and in the contemporary ANTARCTIC[27] and SENIOR (Efficacy and Safety of New Generation Drug Eluting Stents Associated With an Ultra Short Duration of Dual Antiplatelet Therapy: Design of the Short Duration of Dual Antiplatelet Therapy With Synergy II Stent in Patients Older Than 75 Years Undergoing Percutaneous Coronary Revascularization)[29] studies (the latter, however, including >50% stable patients), with all-cause mortality of 6% at 1 year and recurrent MI of < 3% in all 3 studies. Stent thrombosis rates were also lower than those observed in the TRITON-TIMI 38 study, and the numerically lower rate observed with prasugrel than with clopidogrel in the present study did not result in an overall clinical benefit. Thus, it is likely that the improvement in PCI technique and materials resulted in lower ischemic events than in the past in this patient population treated invasively, rendering the use of an aggressive platelet inhibition less beneficial.[1,2,8,9] The exclusion of patients with cardiogenic shock, prior stroke, recent bleeding, and need of oral anticoagulants, as well as the need to obtain informed consent to participate in a randomized trial, may also have resulted in
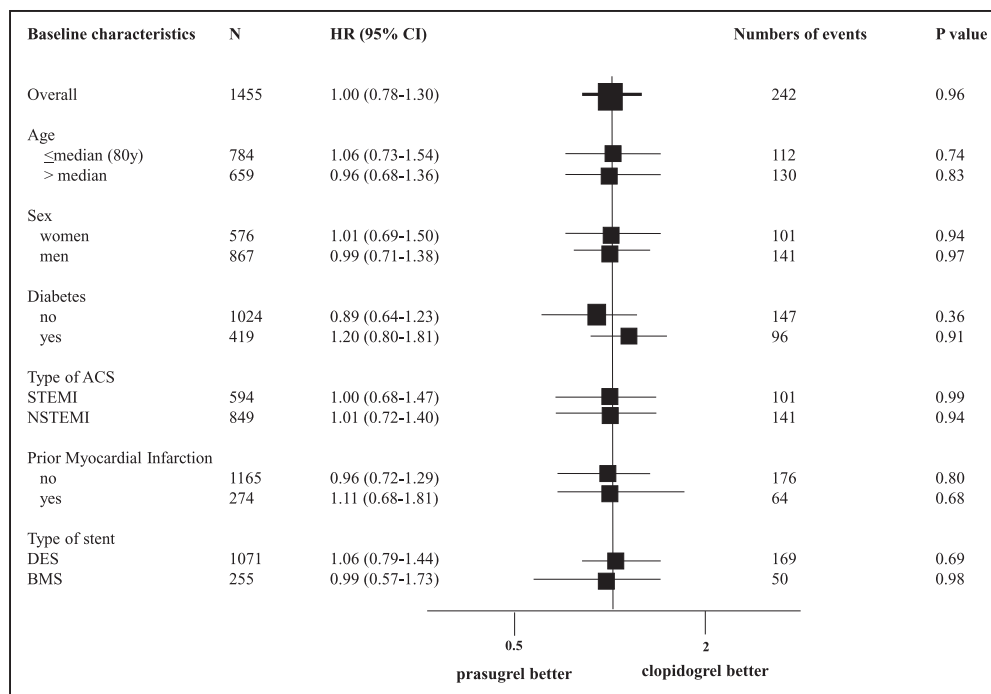
Baseline characteristics	N	HR (95% CI)		Numbers of events	P value
Overall	1455	1.00 (0.78-1.30)		242	0.96
Age					
≤median (80y)	784	1.06 (0.73-1.54)		112	0.74
> median	659	0.96 (0.68-1.36)		130	0.83
Sex					
women	576	1.01 (0.69-1.50)		101	0.94
men	867	0.99 (0.71-1.38)		141	0.97
Diabetes					
no	1024	0.89 (0.64-1.23)		147	0.36
yes	419	1.20 (0.80-1.81)		96	0.91
Type of ACS					
STEMI	594	1.00 (0.68-1.47)		101	0.99
NSTEMI	849	1.01 (0.72-1.40)		141	0.94
Prior Myocardial Infarction					
no	1165	0.96 (0.72-1.29)		176	0.80
yes	274	1.11 (0.68-1.81)		64	0.68
Type of stent					
DES	1071	1.06 (0.79-1.44)		169	0.69
BMS	255	0.99 (0.57-1.73)		50	0.98

0.5
prasugrel better

2
clopidogrel better

Figure 3. Cumulative primary event rates in subgroups.
ACS indicates acute coronary syndrome; BMS, bare metal stents; CI, confidence interval; DES, drug-eluting stents; HR, hazard ratio; NSTEMI, non–ST-segment–elevation myocardial infarction; and STEMI, ST-segment–elevation myocardial infarction.

the selection of a low-risk population compared with real-life populations.

Considering the octogenarian age of patients included in the present trial, bleeding events were relatively low. Part of the reason for this finding may reside in the fact that we had excluded patients with prior stroke, those with recent gastrointestinal or genitourinary bleeding, and those on oral anticoagulants. We had previously observed a similarly lower-than-expected rate of in-hospital bleeding complications in our first Elderly ACS study of patients with NSTE-ACS[6] that we attributed to the large use of the radial approach to PCI. In addition, in the present trial, radial access was used in more than three quarters of patients. A similarly low bleeding rate was observed in the recent SENIOR trial, which used the radial approach in 80% of the cases.[29] Moreover, after discharge, most bleeding complications ascribed to antiplatelet therapy in elderly patients have been shown to be of gastrointestinal origin and to be reduced by concomitant administration of a proton pump inhibitor.[30] Current guidelines[11] and expert consensus documents[31] recommend a proton pump inhibitor in combination with dual antiplatelet therapy in elderly patients at higher risk of bleeding complications on the basis of the results of the COGENT randomized trial (Clopidogrel and the Optimization of Gastrointestinal Events *Trial*), showing nearly halving of gastrointestinal bleeding without affecting ischemic complications.[32] Following these recommendations, concomitant prescription of a proton pump inhibitor became almost ubiquitous in elderly patients on dual antiplatelet therapy[27] and was recommended in all patients in our study protocol.[23]

Study Limitations

The fact that the study was interrupted before reaching the target number of primary events is a limitation of the study. Because we were aware of the continuous improvements in outcomes in the elderly population treated by PCI,[1,2] we had specifically planned an interim analysis to reassess the sample size calculation on the basis of the actual probability of the primary end point after the first 1000 patients had completed 1 year of follow-up. This analysis showed a composite event rate lower than hypothesized on the basis of what had been observed in the Italian Elderly ACS study[6] and a virtually null between-group difference in the primary outcome. This finding was confirmed in the complete cohort of 1443 patients with a median follow-up of 12 months. The final study analysis is underpowered because of a lower-than-expected event rate and a lower-than-planned number of patients enrolled.

CONCLUSIONS

The present study in elderly patients with ACS showed no difference in the primary end point between reduced-dose prasugrel and standard-dose clopidogrel. However, the study should be interpreted in light of the premature termination of the trial. The study adds clini-

cal data to the existing guideline recommendations[12,13] that a reduced 5-mg prasugrel dose can be used as an alternative to clopidogrel in elderly patients with ACS after PCI, although without overall clinical benefit. In terms of actual event rates and complications, the present trial provides original information on the antiplatelet therapy of elderly patients with ACS treated with PCI, reducing the knowledge gaps[33] in this growing population that is still poorly represented in clinical trials.

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APPENDIX

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