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Use of low-dose prasugrel vs. clopidogrel in elderly patients with high clinical and PCI complexity.

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Short title: *Low-dose prasugrel in elderly patients with high clinical and PCI complexity*

***Possible conflicts of interest*:** the authors have no conflicts of interest to declare

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***Portrait of the first author*:**

Classifications: ACS/NSTEACS; elderly (>75); prior myocardial infarction; prior PCI; multiple vessel disease; adjunctive pharmacotherapy.

Abbreviations: *ACS*, Acute Coronary Syndromes; *DAPT*, Dual Antiplatelet Therapy; *MACE*, Major Adverse Cardiovascular Events; *MI*, Myocardial Infarction; *(N)STEMI, (Non) ST-Elevation Myocardial Infarction*; *PCI*, Percutaneous Coronary Intervention:

Introduction

Prasugrel was proven to be superior to clopidogrel in reducing ischemic events in the setting of acute coronary syndromes (ACS) but failed to improve outcomes in elderly patients at higher bleeding risk.[1] Despite elderly patients often present with increased ischemic risk[2] and a more potent $P2Y_{12}$ inhibition was suggested to be preferable in terms of longer dual antiplatelet therapy (DAPT) duration[3,4] or of a potent drug use,[5] evidence supporting the use of prasugrel in this specific subset are lacking. The aim of this paper was to evaluate the impact of high clinical and PCI complexity on the investigational treatment in elderly patients with ACS.

Methods

The Elderly ACS 2 trial[1] (NCT01777503) was a randomized, open-label, blinded endpoint trial carried out at 32 centers in Italy. Eligible were patients older >74 years with ST-segment–elevation myocardial infarction (STEMI) or Non STEMI (NSTEMI) undergoing PCI during the index admission. Participants were randomized to clopidogrel (75 mg daily) or prasugrel (5 mg once daily). We performed a post-hoc subgroup analysis to evaluate the role of coronary atherothrombotic burden as potential effect modifier of the investigational treatment on the outcomes of interest. We hypothesized that the lack of benefit of low-dose prasugrel observed in the pilot study[1] depends on the individual ischemic burden. Explored markers were: *a priori* high ischemic risk profile (defined according to 2019 ESC guidelines on Chronic Coronary Syndromes as diffuse multivessel coronaropathy and medically treated diabetes mellitus or recurrent MI or peripheral vascular disease or chronic kidney disease) and PCI complexity (defined if ≥3 lesions were treated, if ≥3 stents were deployed, or if any bifurcation, trifurcation, chronic total obstruction or moderate-to-severe calcified lesions were treated)[4]. The primary endpoint of the analysis was the composite of mortality, MI, disabling stroke and re-hospitalization for cardiovascular (CV) causes or bleeding. The secondary endpoint was the aggregate of major adverse cardiac events (MACE) including mortality, MI, disabling stroke and re-hospitalization for CV causes. Safety endpoints were all-cause mortality and any bleeding event. Follow-up was censored at 1-year.

Results

Of the 1,443 enrolled subjects, 605 (41.9%) underwent complex PCI (**Supplementary Table 1**) and 1,025 (71.0%) presented with a high ischemic risk profile; neither of these were associated with worse outcome in terms of primary endpoint (p=0.21 and p=0.11, respectively; **Supplementary Figure 1**). Among those who underwent complex PCI, 309 (51.1%) were randomized to receive low-dose prasugrel and 296 (48.9%) clopidogrel while 502 (48.9%) of those with high ischemic

risk profile were randomized to low-dose prasugrel and 523 (51.1%) to clopidogrel; baseline characteristics were well balanced according to randomization arm. Similar rates of primary endpoint were observed irrespective of the randomization arm in patients with complex PCI features (low-dose prasugrel arm 19.4% vs. clopidogrel arm 16.9%; Hazard Ratio [HR] 1.14; 95% Confidence Interval [CI] 0.8-1.7; *p*=0.48) and with high ischemic risk features (18.1% vs. 17.2%; HR 1.04; 95% CI 0.8-1.4; *p*=0.82). Other results of survival analysis are shown in **Supplementary Table 2**; of note, a tendency towards more bleedings was observed in high ischemic risk patients receiving low-dose prasugrel (5% vs. 2.7%; HR: 1.82; 95% CI: 0.95-3.5; *p*=0.07). Therefore, neither complex PCI nor high ischemic risk were found to be effect modifiers on the primary endpoint (interaction *p*: 0.34 and 0.68 respectively, **Figure 1**). This finding was consistent among secondary and safety endpoints MACE (interaction *p*: 0.18 and 0.73, respectively), all-cause death (interaction *p*: 0.36 and 0.43, respectively) and bleedings (interaction *p*: 0.76 and 0.26, respectively).

Discussion

The main findings of this study are as follow:

1. In a cohort of elderly patients admitted for ACS no significant impact of high clinical nor PCI complexity was found on clinical endpoints at 1 year;
2. $P2Y_{12}$ inhibition with low-dose prasugrel had comparable results vs. standard clopidogrel treatment regardless of PCI complexity or of high ischemic risk;
3. A non-significant trend towards more bleeding was observed with low-dose prasugrel administration when high coronary atherothrombotic burden was present.

Elderly patients are underrepresented in clinical trials and therefore an age-specific evidence-based clinical strategy is often lacking. Awaited results from the POPULAR-AGE trial showed that full-dose prasugrel and ticagrelor might be associated with similar results in terms of ischemic endpoints in elderly subjects (Gimbel et al., *presented at ESC 2019*) but the relative importance of high ischemic burden remains unclear in this setting. In the present subgroup analysis, no effect modification of high ischemic risk profile nor of PCI complexity was found on the administration of investigational treatment. No benefit of low-dose prasugrel vs. standard clopidogrel was observed in terms of clinical and ischemic endpoints in our cohort of elderlies at high ischemic risk nor in those who underwent complex PCI. Considering the high prevalence of high ischemic risk profile and complex PCI features in the elderly population, the interpretation of ischemic risk in the elderly might not be straightforward. First, previous studies stratified the benefit of longer DAPT duration according to ischemic risk as measured by PCI complexity but without including age for risk

adjustment.[3] As patients with complex PCI features are often older,[2] this might represent an important confounder and complex PCI may not be appropriate for ischemic risk stratification in the elderlies. Second, considering the prevalence of other inherent comorbidities (such as atrial fibrillation, anemia, chronic lung disease, renal and liver dysfunction, etc.) in elderly subjects, secondary mechanisms of myocardial ischemia might play a major role over primary mechanisms of atherothrombosis. This might contribute to blunt the benefit of potent antithrombotic drugs such as prasugrel which still carry a higher likelihood of bleedings. In fact, a non-significant increase in bleeding events was observed in elderly subjects with high ischemic risk profile randomized to low-dose prasugrel. Third, our results reinforce the need for appropriate risk stratification in this population which has not yet been addressed by dedicated external validation initiatives. In fact, conditions inherent to aging pose elderly patients at a peculiar bleeding risk and variables which stratify for high ischemic risk also identify patients at higher bleeding risk. In conclusion, even if prasugrel might represent an option for elderly patients with ACS and high clinical or PCI complexity, it should be prescribed considering the individual bleeding risk profile

Limitations

First, our study was a non-pre-specified post-hoc subgroup analysis and our neutral results might reflect those of the pilot study. Second, the main trial was interrupted before complete enrollment of patients and might be underpowered to detect differences between smaller subgroups. Therefore, our conclusions should be generalized with caution and are mainly hypothesis-generating.

Conclusions

In elderly patients presenting with ACS and high clinical or PCI complexity low-dose prasugrel is comparable to clopidogrel but it should be prescribed in the light of the individual bleeding risk profile.

Impact on daily practice: *Low-dose prasugrel is an evidence-based option in elderly patients presenting with acute coronary syndromes and high clinical or PCI complexity. Nonetheless, no benefit was observed vs. clopidogrel in terms of clinical outcomes. Higher bleeding risk should be taken into consideration when prescribing low-dose prasugrel.*

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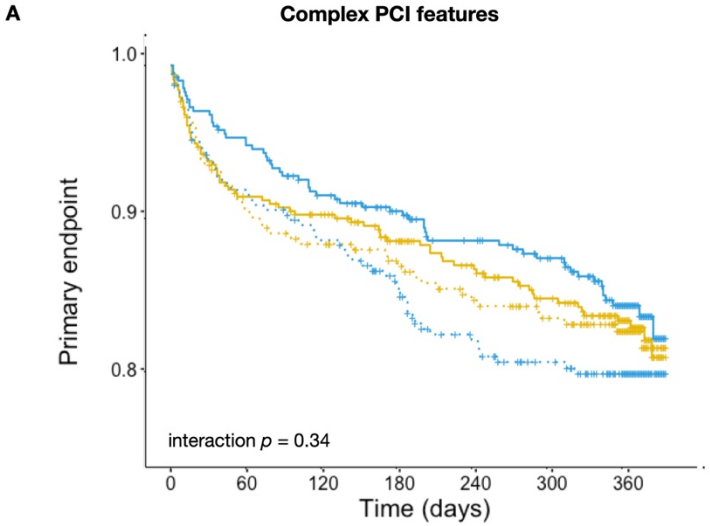
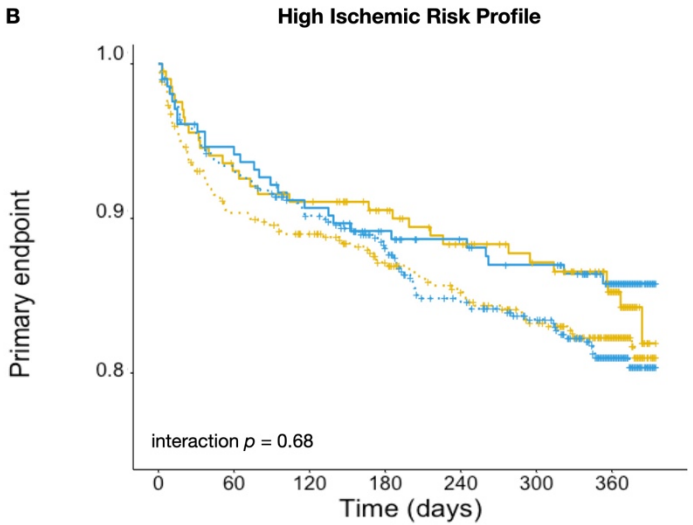
Figure Legend

Figure 1. Survival analysis of primary endpoint at follow-up according to randomization arm and PCI complexity (A) and ischemic risk profile (B).



Number at risk

Clopidogrel + Non-complex PCI	434	391	380	352	328	306	255
Clopidogrel + Complex PCI	296	262	252	240	225	211	179
Prasugrel + Non-complex PCI	404	382	360	340	316	300	242
Prasugrel + Complex PCI	309	281	268	250	229	213	178



Number at risk

Clopidogrel + Non-High Ischemic Risk	204	187	181	168	157	147	124
Clopidogrel + High Ischemic Risk	523	464	449	422	395	370	310
Prasugrel + Non-High Ischemic Risk	206	192	183	171	161	155	130
Prasugrel + High Ischemic Risk	502	466	441	415	381	355	287

Online Data Supplement

Supplementary Table 1. Baseline characteristics.

Supplementary Table 2. Event Rates.

Supplementary Figure 1. Supplementary Figure 1. Survival analysis of primary endpoint at follow-up according to PCI complexity (A) and high ischemic risk profile (B).

Supplementary Table 1. Baseline characteristics.

		Complex PCI	Non-complex PCI		High Ischemic Risk [a]	Non High Ischemic Risk	
	Overall N=1,443	**Overall N = 605**	**Overall N = 838**	***p* value**	***Overall N = 1,025***	***Overall N = 410***	***p* value**
Age (y)	80.00 [77, 84]	80.00 [77, 83]	80.00 [77, 84]	0.215	80.00 [77, 84]	80.00 [77, 83]	0.845
BMI (kg/m^2)	26.01 (3.82)	26.01 (3.92)	26.01 (3.68)	0.994	633 (61.8)	229 (55.9)	0.045
Male sex	867 (60.1)	365 (60.3)	502 (59.9)	0.914	26.06 (3.88)	25.90 (3.64)	0.465
Presenting with STEMI	595 (41.2)	323 (53.4)	272 (32.5)	<0.001	401 (39.1)	190 (46.3)	0.014
Diabetes	253 (17.5)	94 (15.5)	159 (19.0)	0.104	199 (19.4)	53 (12.9)	0.004
Known Cancer	45 (3.1)	15 (2.5)	30 (3.6)	0.301	28 (2.7)	16 (3.9)	0.321
LVEF (%)	48.27 (9.59)	47.26 (9.54)	49.08 (9.55)	0.002	47.86 (9.62)	49.37 (9.37)	0.019
eGFR (mL/min/1.73 m^2)	68.82 (22.65)	68.50 (23.05)	69.06 (22.36)	0.656	67.25 (23.18)	72.86 (20.71)	<0.001
Family history of CVD	215 (14.9)	84 (13.9)	131 (15.6)	0.398	150 (14.6)	64 (15.6)	0.699
Hypertension	1120 (77.6)	463 (76.5)	657 (78.4)	0.437	798 (77.9)	316 (77.1)	0.802
Hypercholesterolemia	644 (44.6)	258 (42.6)	386 (46.1)	0.217	471 (46.0)	170 (41.5)	0.137
COPD	87 (6.0)	35 (5.8)	52 (6.2)	0.827	59 (5.8)	27 (6.6)	0.635
Liver disease	24 (1.7)	10 (1.7)	14 (1.7)	1.000	12 (1.2)	12 (2.9)	0.034
History of stroke	1 (0.1)	0 (0.0)	1 (0.1)	1.000	1 (0.1)	0 (0.0)	1.0
History of MI	274 (19.0)	103 (17.0)	171 (20.4)	0.122	226 (22.0)	47 (11.5)	<0.001
Previous PCI	264 (18.3)	94 (15.5)	170 (20.3)	0.026	205 (20.0)	58 (14.1)	0.012
Previous CABG	128 (8.9)	65 (10.7)	63 (7.5)	0.042	115 (11.2)	13 (3.2)	<0.001

Peripheral Vascular Disease	125 (8.7)	54 (8.9)	71 (8.5)	0.836	65 (6.3)	56 (13.7)	<0.001
History of Atrial Fibrillation	56 (3.9)	20 (3.3)	36 (4.3)	0.411	41 (4.0)	15 (3.7)	0.880
Number of diseased vessels	2.29 (1.06)	2.38 (1.05)	2.22 (1.06)	0.005	2.75 (0.85)	1.13 (0.51)	<0.001
Number of Implanted stents	1.14 (0.64)	1.34 (0.72)	0.99 (0.52)	<0.001	1.14 (0.63)	1.12 (0.65)	0.579
Number treated lesions	1.14 (0.64)	1.34 (0.72)	0.99 (0.52)	<0.001	1.14 (0.63)	1.12 (0.65)	0.579
Any Treated Bifurcation	229 (15.9)	229 (37.9)	0 (0.0)	<0.001	188 (18.3)	41 (10.0)	<0.001
Any Treated CTO	400 (27.7)	400 (66.1)	0 (0.0)	<0.001	287 (28.0)	113 (27.6)	0.918

Data are expressed as *n* (valid %) or median [IQR]. Creatinine Clearance (*CrCl*) calculated with the MDRD formula.

[a] Defined according to 2019 ESC Guidelines on Chronic Coronary Syndromes as diffuse multivessel coronaropathy with at least one of the following: diabetes mellitus requiring medication, recurrent MI, peripheral vascular disease or CKD with eGFR 15-59 mL/min/1.73 m^2.

ACS, Acute Coronary Syndrome; *AF*, Atrial Fibrillation; *BMI*, Body Mass Index; *CABG*, Coronary Artery Bypass Graft; *COPD*, Chronic Obstructive Pulmonary Disease; *CTO*, Chronic Total Obstruction; *CVD*, Cardiovascular Disease; *LVEF*, Left Ventricular Ejection Fraction; *MI*, Myocardial Infarction; *PCI*, Percutaneous Coronary Intervention; *STEMI*, ST-Elevation Myocardial Infarction.

Supplementary Table 2. Event Rates.

	Complex PCI					Non-complex PCI		
	Overall N = 605	**Prasugrel subgroup N = 309**	**Clopidogrel subgroup N = 296**	**HR (95% CI)**	***p* value**	**Overall N =838**	**HR (95% CI)**	***p* value**
Primary endpoint	110 (18.1)	60 (19.4)	50 (16.9)	1.14 (0.79-1.67)	0.48	132 (15.7)	1.175 (0.91-1.51)	0.21
MACE	97 (16.0)	53 (17.2)	44 (14.9)	1.19 (0.79-1.78)	0.40	112 (13.4)	1.12 (0.92-1.59)	0.16
All-cause death	46 (7.6)	22 (7.1)	24 (8.1)	0.85 (0.47-1.52)	0.59	44 (5.3)	1.45 (0.96-2.2)	0.07
Bleeding	15 (2.5)	10 (3.2)	5 (1.7)	1.86 (0.64-5.46)	0.25	32 (3.8)	0.65 (0.35-1.2)	0.17
	High Ischemic Risk [a]					**No High Ischemic Risk**		
	N = 1,025	**N=502**	**N=523**	**HR (95% CI)**	***p* value**	**N = 410**	**HR (95% CI)**	***p* value**
Primary Endpoint	181 (17.6)	91 (18.1)	90 (17.2)	1.04 (0.78-1.4)	0.82	58 (14.1)	1.27 (0.95-1.7)	0.11
MACE	152 (14.8)	76 (15.1)	76 (14.5)	1.02 (0.74-1.4)	0.89	49 (12.0)	1.26 (0.921-1.73)	0.16
All-cause death	67 (6.5)	32 (6.4)	35 (6.7)	0.9 (0.58-1.5)	0.78	22 (5.3)	1.23 (0.76-2.0)	0.39
Bleeding	39 (3.8)	25 (5.0)	14 (2.7)	1.82 (0.95-3.5)	0.07	7 (1.7)	2.27 (1.02-5.07)	0.04

[a] Defined according to ESC 2019 Guidelines on Chronic Coronary Syndromes as diffuse multivessel coronaropathy with at least one of the following: diabetes mellitus requiring medication, recurrent MI, peripheral vascular disease or eGFR 15-59 mL/min/1.73 m^2.

CI, Confidence Interval; *HR*, Hazard Ratio; *MACE*, Major Adverse Cardiovascular Events; *PCI*, Percutaneous Coronary Intervention.

Supplementary Figure 1. Survival analysis of primary endpoint at follow-up according to PCI complexity (A) and high ischemic risk profile (B). Log rank *p* are shown.