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Percutaneous coronary intervention reduces mortality in myocardial infarction patients with comorbidities: Implications for elderly patients with diabetes or kidney disease☆,☆☆

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ABSTRACT

Background: Percutaneous coronary intervention (PCI) reduces mortality in most myocardial infarction (MI) patients but the effect on elderly patients with comorbidities is unclear. Our aim was to analyse the effect of PCI on in-hospital mortality of MI patients, by age, sex, ST elevation on presentation, diabetes mellitus (DM) and chronic kidney disease (CKD).

Methods: Cohort study of 79,791 MI patients admitted at European hospitals during 2000–2014. The effect of PCI on in-hospital mortality was analysed by age group (18–74, ≥75 years), sex, presence of ST elevation, DM and CKD, using propensity score matching. The number needed to treat (NNT) to prevent a fatal event was calculated. Sensitivity analyses were conducted.

Results: PCI was associated with lower in-hospital mortality in ST and non-ST elevation MI (STEMI and NSTEMI) patients. The effect was stronger in men [Odds ratio (95% confidence interval) 0.30 (0.25–0.35)] than in women [0.46 (0.39–0.54)] aged ≥75 years, and in NSTEMI [0.22 (0.17–0.28)] than in STEMI patients [0.40 (0.31–0.5)] aged <75 years. PCI reduced in-hospital mortality risk in patients with and without DM or CKD (54–72% and 52–73% reduction in DM and CKD patients, respectively). NNT was lower in patients with than without CKD [≥75 years: STEMI = 6(5–8) vs 9(8–10); NSTEMI = 10(8–13) vs 16(14–20)]. Sensitivity analyses such as exclusion of hospital stays <2 days yielded similar results.

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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Conclusions: PCI decreased in-hospital mortality in MI patients regardless of age, sex, and presence of ST elevation, DM and CKD. This supports the recommendation for PCI in elderly patients with DM or CKD.

1. Introduction

Current guidelines recommend percutaneous coronary intervention (PCI) for most patients with ST elevation acute myocardial infarction (STEMI) or with non ST elevation acute coronary syndrome (NSTEACS) [1–3]. In STEMI, PCI is advised in all patients in the first 12 h after symptom onset, the earlier the better [1,2]. In NSTEACS, the treatment strategy is to perform PCI during the first 72 h if patients have at least one intermediate risk criterion such as diabetes mellitus (DM), chronic kidney disease (CKD), or reduced left ventricular ejection fraction, among others [3].

The recommendation stands for elderly patients (aged 75 years and older), as it has been shown that STEMI and NSTEACS patients have reasonable outcomes when treated invasively [4–7]. In elderly acute coronary syndrome (ACS) patients, individual circumstances including life expectancy, quality of life, and comorbidities should also be taken into account [2,6,8–11]. While comorbidities are one of the decisional factors that determine an invasive strategy in elderly ACS patients, there is no specific advice concerning elderly patients with comorbidities in current guidelines.

Two of the most common comorbidities in elderly ACS patients are DM and CKD, each one affecting 20–30% of this population [12]. Management of STEMI patients with DM should be the same as for individuals without DM [2]. In NSTEACS patients with DM, an invasive strategy is recommended over non-invasive management [3]. Advisement on managing CKD is only available for NSTEACS patients, in which coronary angiography and revascularization, if needed, are recommended after assessment of benefits, risks, and the severity of renal dysfunction [3,13]. There are no studies comparing survival outcomes after revascularization in elderly ACS patients with and without DM and only one small study has analysed revascularization and mortality in association with renal function in elderly NSTEACS patients [14].

The goal of this study was to provide robust data on the effect of PCI on in-hospital mortality risk in patients with myocardial infarction (MI) with and without ST elevation, by age group, sex, and presence of DM or CKD.

2. Methods

2.1. Data source

The EUROTRACS (EUROpean Treatment & Reduction of Acute Coronary Syndromes cost analysis) database contains data on 94,474 ACS patients admitted in European hospitals during 2000–2014. The EUROTRACS database includes 3 European registries of ACS patients (EURHOBOP [15] – EURopean Hospital Benchmarking by Outcomes in ACS Processes-, Euro Heart Survey I [16] and Euro Heart Survey II [17]), and 6 national/regional registries (Greek HELIOS [18] –Hellenic Infarction Observation Study- MI registry; regional health information system from Lazio [19], Italy; Spanish MASCARA [20] – Manejo del Síndrome Coronario Agudo. Registro Actualizado- ACS registry; MONICA/KORA [21] MI registry from Augsburg, Germany; REGICOR [22] – REgistre GIroní del COR- MI registry from Girona, Spain; and the Italian MCH-ESREFO [23] registry). Main characteristics of the registries are described in Suppl. Table 1. The EUROTRACS Study was approved by the Hospital del Mar review committee.

2.2. Design and study population

This was a cohort study of patients from the EUROTRACS database designed as a matched analysis by a propensity score (PS) for PCI use. Patients were followed during their hospital stay for the occurrence of all-cause mortality. We included all EUROTRACS component registries with information on diagnosis and on the required covariates, and selected patients aged ≥18 years with a diagnosis of MI. As shown in Suppl. Fig. 1 79,791 MI patients were included.

2.3. Study variables

The primary outcome of the study was in-hospital mortality and the exposure of interest was use of PCI during hospitalization, independently of the type (primary, rescue, elective, other) and the time since onset of symptoms. Other variables of interest included age, sex, initial presence of ST elevation, DM, and CKD. Age was categorized in 2 groups: 18–74 and ≥75 years. Presence of DM was based on previous history, and CKD was based on previous history and on the estimated glomerular filtration rate (eGFR). The eGFR was calculated with admission creatinine using the 4-component Modification of Diet in Renal Disease equation [24]. CKD was assumed if previous history or if the eGFR was <60 mL/min/1.73 m^2.

2.4. Potential confounders of PCI use

To select potential confounders of PCI use to construct the PS, we explored the association of pre-PCI variables with PCI use and with the outcome (in-hospital mortality). We selected all available pre-PCI variables associated with PCI use and in-hospital mortality once variables with excessive missing values were excluded from statistical analysis. Ten variables were selected: age, sex, hypertension, DM, CKD, previous history of MI, admission Killip class, initial presence of ST elevation, year of treatment (categorized in 3 groups: 2000–2004, 2005–2009 and 2010–2014), and hospital characteristics such as university hospital, on-site catheterization laboratory and coronary surgery.

2.5. Statistical analysis

Variables with >50% of missing values in the EUROTRACS database and/or 100% missing in any of the component registries were excluded from the analysis. The remaining variables had <4% of missing data in the EUROTRACS database. Missing data was completed with 20 multiple imputations by chained equations [25]. Analyses were carried out in the 20 multiple imputed datasets and then estimates were combined.

Demographic and clinical data were summarized by the mean and standard deviation (SD) or by frequencies for continuous (normally distributed) or categorical variables, respectively. Means and frequencies were compared between groups using ANOVA or chi-squared tests, respectively.

Four separate analyses were undertaken to examine the in-hospital mortality risk of patients who received PCI compared to those who did not: by age group and sex; by age group and ST elevation; by age group, ST elevation, and DM; and by age group, ST elevation, and CKD.

The PS was computed as the predicted values of PCI use from a logistic regression model taking the selected potential confounders as the predictor variables. The variables used to stratify risk (age, sex, ST elevation, DM, and CKD, depending on the analysis) were not included in the PS used in the specific stratified analysis. Every patient receiving PCI was matched with one patient who did not receive PCI, according to their PS values within a caliper of 0.2 of the logit-transformed PS SD [26]. Balance of covariates was assessed by computing the standardized differences between patients who did or did not receive PCI [27].

In-hospital mortality and its 95% confidence interval (CI) were calculated for each group under analysis. The odds ratio (OR) of in-hospital mortality and its 95% CI for patients receiving PCI compared to the rest were calculated using conditional logistic regression. These models were adjusted for the variables not sufficiently balanced after PS matching (standardized difference > 10%). In-hospital mortality estimates and ORs between groups were compared using the chi-square test and z-scores, respectively, and adjusted for multiple comparisons with the Bonferroni correction.

The number needed to treat (NNT) to prevent one in-hospital death was calculated as the inverse of the absolute risk reduction as follows: $1/(M_{nonPCI} - M_{PCI})$, where M_{nonPCI} and M_{PCI} are the average in-hospital mortality rates predicted by a non-conditional logistic model as if all individuals received PCI and as if none of them received PCI, respectively. Matched pairs were introduced in the non-conditional model as a random effects factor.

Several sensitivity analyses were carried out. First, patients who stayed <2 days at the hospital were excluded. Second, stratification was used instead of matching. OR of in-hospital mortality for patients receiving PCI compared to the rest were obtained by PS tertile, age group (18–59, 60–69, 70–79, and >79 years), and sex/ST elevation using mixed effects logistic regression. PS models included the same variables as the PS of the main analysis except for age. Models for in-hospital mortality included PCI use, the specific PS (logit-transformed), age, thrombolysis, coronary artery bypass grafting (CABG), and maximum Killip class during hospitalization as fixed effects, and country as a random effect. Finally, analyses were undertaken using non-conditional instead of conditional

Table 1
Demographic and clinical characteristics of the study population by age group.

	<75 years (n = 51,747)	≥75 years (n = 28,044)	p-Value
Age	60.4 ± 9.8	82.2 ± 5.2	<0.001
Sex: Female	22.9%	49.1%	<0.001
Diabetes	17.8%	20.8%	<0.001
Hypertension	34.9%	37.7%	<0.001
Chronic kidney disease	7.4%	13.5%	<0.001
Previous MI	15.3%	19.6%	<0.001
Admission Killip class: III-IV	3.8%	7.1%	<0.001
Type of MI			<0.001
STEMI	52.2%	37.3%	
NSTEMI	44.6%	56.0%	
Non-classifiable	3.2%	6.7%	
On-site catheterization laboratory	79.7%	70.1%	<0.001
On-site cardiac surgery department	42.5%	30.0%	<0.001
University hospital	36.1%	26.7%	<0.001
Admission year			<0.001
2000–2004	20.1%	12.3%	
2005–2009	31.9%	27.0%	
2010–2014	48.0%	60.7%	
Thrombolysis	11.8%	4.3%	<0.001
PCI	56.7%	31.4%	<0.001
CABG	4.0%	1.3%	<0.001
Maximum Killip class: III-IV	4.4%	7.5%	<0.001
In-hospital mortality	4.4%	14.9%	<0.001

All variables are presented as percentages except for age, which is presented as mean and standard deviation. CABG, coronary artery bypass grafting; NSTEMI, non ST-elevation myocardial infarction; MI, myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.

logistic regression, and adjusting the in-hospital mortality models for moderators such as thrombolysis, CABG, and maximum Killip class during hospitalization.

All analyses were performed with the R statistical software (version 3.2.3) [28].

3. Results

3.1. Baseline characteristics and matching

Demographic and clinical data by age group are presented in Table 1. Patients aged ≥75 years had a higher prevalence of DM, hypertension, CKD, previous MI, and cardiogenic shock or acute pulmonary edema on admission, compared to younger patients. Older MI patients were more frequently admitted with non-ST elevation MI (NSTEMI). The proportion of patients who received revascularization or were admitted at a centre with an on-site catheterization laboratory was lower in patients aged ≥75 years, compared to younger patients. Patient characteristics by registry are described in Suppl. Table 2.

From the 79,791 patients who fulfilled the inclusion criteria of the study, a median of 64% was matched by PS (interquartile range, 53–70%), depending on the subgroup under analysis. Number of individuals by group before and after matching is shown in Suppl. Table 3.

3.2. In-hospital mortality

Crude in-hospital mortality was significantly lower in men than in women in patients regardless of age (Suppl. Table 4). STEMI patients had higher in-hospital mortality than NSTEMI in both age groups. STEMI patients with DM had higher in-hospital mortality than patients without DM regardless of the age group, while NSTEMI patients with DM had a significantly higher in-hospital mortality only in patients aged <75 years (Suppl. Table 4). Both STEMI and NSTEMI patients with CKD had significantly higher in-hospital mortality than patients without CKD in both age groups.

3.3. Effect of PCI on in-hospital mortality risk

PCI use significantly decreased in-hospital mortality risk in MI patients regardless of age group, sex and ST characteristics (Fig. 1). Men and women younger than 75 years benefited similarly from PCI use, while the risk reduction was significantly larger in men aged ≥75 years compared to women of the same age (70% [65–75%] vs 54% [46–61%], *p*-value <0.001). The in-hospital mortality risk reduction due to PCI use was similar in STEMI and NSTEMI patients aged ≥75 years but was significantly larger in younger patients with NSTEMI, compared to STEMI (78% [72–83%] vs 60% [50–69%], p-value <0.001).

Fig. 2 shows the ORs of in-hospital mortality by presence of DM and CKD and age group for STEMI and NSTEMI patients. The use of PCI significantly decreased in-hospital mortality risk across all variables: STEMI and NSTEMI patients with and without DM or CKD, in both age groups.

3.4. Number needed to treat

NNTs to prevent one in-hospital death by age group, sex, ST elevation, and presence of DM or CKD are shown in Fig. 3. NNTs were significantly lower in STEMI than in NSTEMI patients [<75 years: 24(21–29)

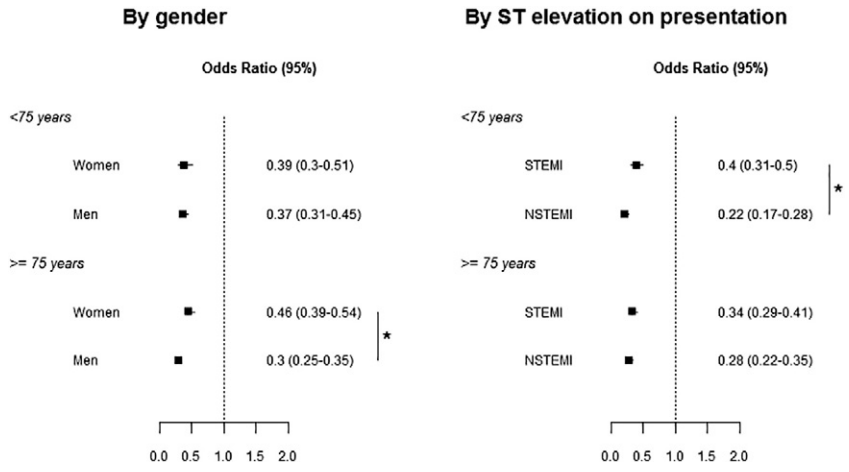

Fig. 1. Effect of percutaneous coronary intervention on in-hospital mortality risk by age group, sex, and ST elevation on presentation. NSTEMI, non ST elevation myocardial infarction; STEMI, ST elevation myocardial infarction. * indicates statistical significance. Significance was adjusted for multiple comparisons and assumed when <0.0025.

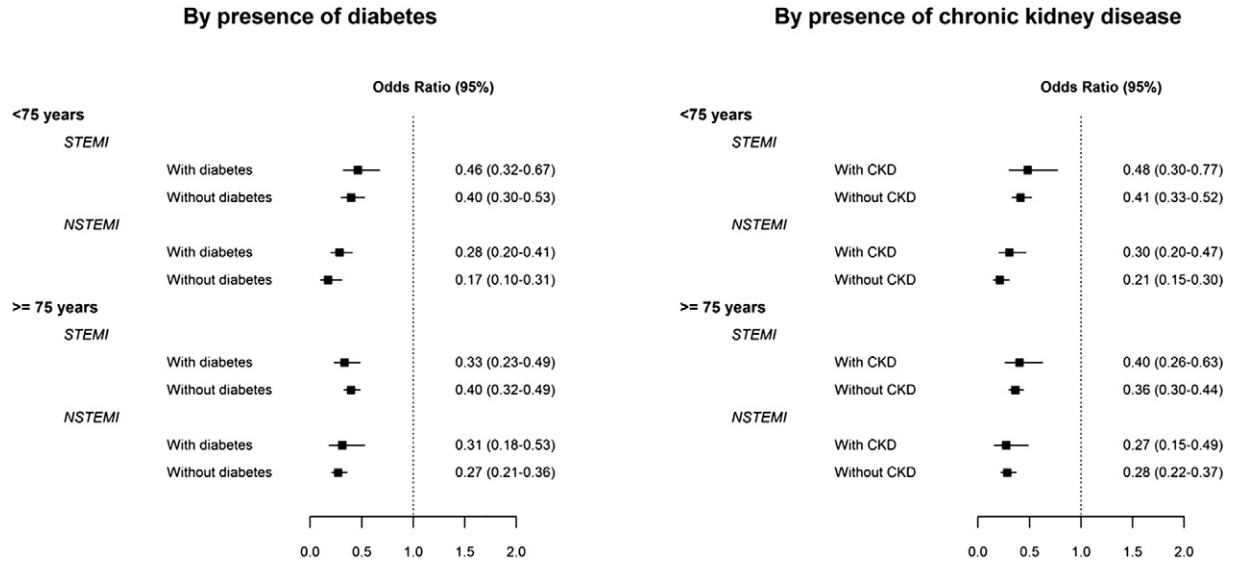

Fig. 2. Effect of percutaneous coronary intervention on in-hospital mortality risk by age group, ST elevation on presentation and presence of diabetes mellitus or chronic kidney disease. CKD, chronic kidney disease; NSTEMI, non ST elevation myocardial infarction; STEMI, ST elevation myocardial infarction.

vs 35(32–39); ≥75 years: 8(7–8) vs 14(13–16)] and similar in men and women (Fig. 3A). As for patients with and without DM, NNTs were lower in patients with DM in NSTEMI patients aged <75 years (21 (19–25) vs 40 (35–46)) (Fig. 3B). NNTs were also significantly lower in patients with CKD than in those without CKD in STEMI and NSTEMI patients younger than 75 years [STEMI: 10(8–14) vs 27(22 − 33);

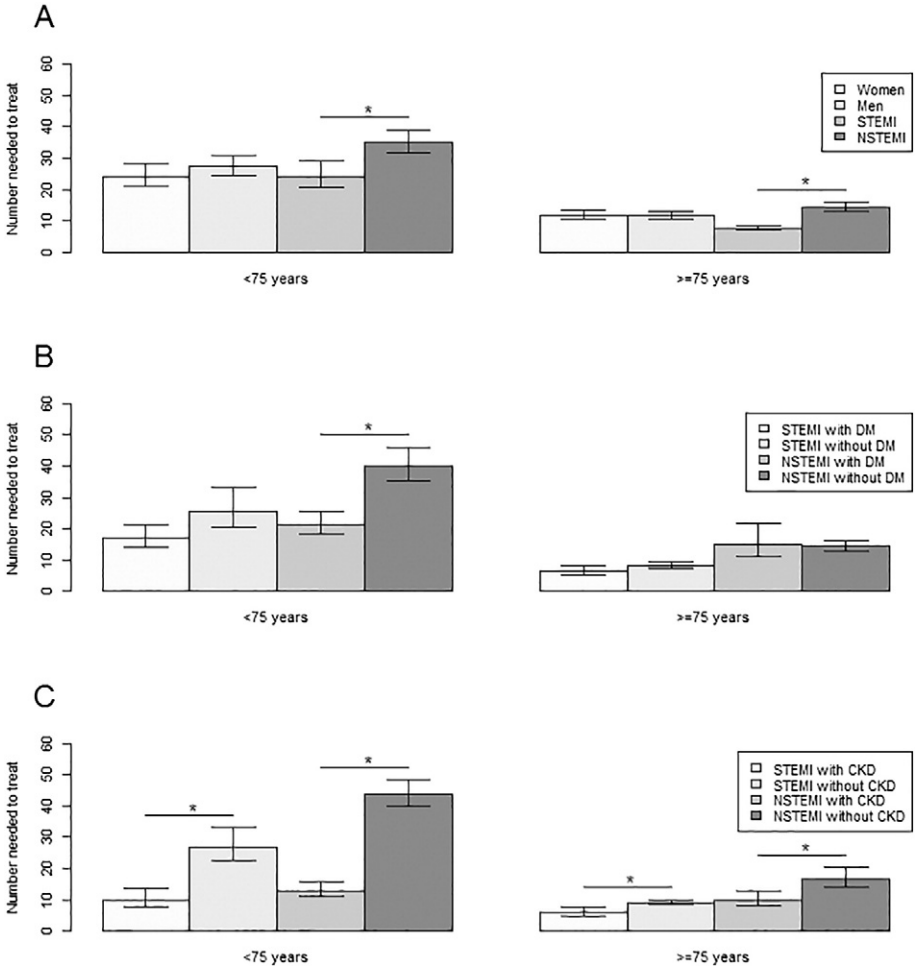

Fig. 3. Number needed to treat (NNT) to avoid one in-hospital death. NNT by age group, sex, and ST elevation on presentation (A); NNT by age group, ST elevation on presentation and diabetes mellitus (B); NNT by age group, ST elevation on presentation and chronic kidney disease (C) in patients with myocardial infarction from the EUROTRACS database. DM, diabetes mellitus; CKD, chronic kidney disease; NSTEMI, non ST elevation myocardial infarction; STEMI, ST elevation myocardial infarction. * indicates statistical significance.

NSTEMI: 13(11–16) vs 44(40–48)] and ≥75 years [STEMI: 6(5–8) vs 9(8–10); NSTEMI: 10(8–13) vs 16(14–20)] (Fig. 3C).

3.5. Sensitivity analyses

Exclusion of hospital stays shorter than 2 days resulted in similar OR for in-hospital mortality in all subgroups (Suppl. Figs. 2 and 3). Stratification analyses showed that PCI use decreased in-hospital mortality risk in MI patients in the 4 age groups analysed regardless of sex and initial presence of ST elevation. Only in 2 groups (women aged 18–59 years in the 1st PS tertile and NSTEMI patients aged 18–59 years in the 3rd PS tertile) PCI did not significantly decrease in-hospital mortality risk (Suppl. Figs. 4 and 5). Non-conditional regression analysis and models with moderators showed similar results compared to the main analyses (Suppl. Tables 5 and 6).

4. Discussion

The analysis of 79,791 contemporary European MI patients showed that PCI use was associated with lower in-hospital mortality. This association was observed in both men and women and in patients with STEMI and NSTEMI, becoming significantly larger in men than in women in the group aged ≥75 years, while the effect was larger in NSTEMI than in STEMI patients aged <75 years. PCI use was associated with lower in-hospital mortality in patients with and without DM and in those with and without CKD, independently of age group and ST elevation. In addition, the NNT for patients with CKD compared to those without CKD was lower in all age groups in STEMI and NSTEMI patients, and in NSTEMI patients younger than 75 years the NNT was lower for DM than for non-DM patients.

In accordance with our results, a number of studies in the last decade have shown that an invasive strategy or PCI use is associated with lower in-hospital to 1-year mortality in both younger and elderly patients with ACS [5–11,29–32]. A subgroup analysis of elderly patients with STEMI in 11 randomized trials showed a reduction in 30-day mortality in patients older than 70 years receiving primary PCI (PPCI) compared to thrombolysis [29]. In a more recent trial, a trend towards a reduction in 30-day mortality was found for PPCI compared to thrombolysis in patients older than 75 years [7]. Similarly, in the MINAP registry, an invasive versus conservative strategy reduced the risk of 1-year mortality in both younger and elderly patients [29]. Our results point in the same direction, showing lower in-hospital mortality of STEMI patients aged <75 and ≥75 years who received PCI versus no PCI.

As for NSTEMI patients, an invasive strategy was associated with lower in-hospital and 1-year mortality in patients ≥75 years from a German ACS registry [8]. In this registry, there was no in-hospital mortality benefit in women receiving an invasive strategy [33]. Our analysis showed a benefit in both men and women, although in the oldest patients (aged ≥75 years) the effect was significantly larger in men. The larger effect in older men could be due to the more atypical symptoms in older women and the reported delay in their post-MI hospital admission [34,35]. Investigators from the GRACE and MINAP registries and a recent clinical trial have also found that an invasive strategy reduced 6-month and 1-year mortality, as well as a composite outcome of MI, need for urgent revascularization, stroke and death, in elderly NSTEACS patients [10,31,36]. Our results also showed lower in-hospital mortality in NSTEMI patients who received PCI, independently of age.

In contrast to the GRACE and MINAP results [10,31], we did not find a smaller effect in the oldest age group (≥75 years). This difference may be due to new guideline-recommended medications (antiplatelet agents, statins, beta-blockers and angiotensin converting enzyme inhibitors/angiotensin receptor blockers [ACEIs/ARBs]) [30] being available to the patients included in our study, which in turn would yield fewer complications and better outcomes. In addition, the introduction of PCI trans-radial arterial access, particularly in ST elevation ACS patients, would reduce access site complications, which are a major cause of mortality after PCI in elderly patients [37].

It is intriguing that PCI had a larger effect on reducing in-hospital mortality in patients younger than 75 years with NSTEMI, compared to patients with STEMI, in our study. Several factors likely influenced this result. On the one hand, STEMI is associated with a higher risk of in-hospital mortality than NSTEMI [38], and unsuccessful PCI has a larger impact on mortality in STEMI than in NSTEMI [39]. On the other hand, it is possible that patients with STEMI in our sample were in worse condition than NSTEMI patients, as the proportion of patients presenting with cardiogenic shock or pulmonary oedema on admission was higher in STEMI than in NSTEMI (5.21 vs 3.77%, p-value < 0.001).

Our results showing a protective effect of PCI on in-hospital mortality in individuals with and without DM are in line with current STEMI and NSTEACS guidelines [2,3], which recommend similar management of patients with and without DM. Our data also provide new evidence for the consideration of PCI in elderly patients with DM. Our results are in accordance with a meta-analysis of randomized trials, which showed that an invasive strategy reduced cardiovascular events similarly in diabetic and non-diabetic patients with NSTEACS at 12-month follow-up and that the reduction of recurrent nonfatal MI was greater in patients with DM [40].

In the analysis of patients with and without CKD, a protective effect of PCI on in-hospital mortality was observed in both groups. In a Swedish nationwide register, better 1-year survival was also observed in NSTEMI patients younger than 80 years undergoing invasive therapy, particularly in individuals with mild-to-moderate renal insufficiency [13]. A small prospective study also showed that coronary revascularization decreases the risk of 1-year mortality in elderly patients with NSTEACS independently of creatinine clearance [14]. Our results reinforce the findings in the elderly population with NSTEMI and provide new evidence for the consideration of PCI in STEMI patients regardless of age, despite a lack of relevant recommendations in current guidelines.

4.1. Study limitations

The present analysis is an observational study, which could affect the reliability of results due to selection and survival bias, among others. Efforts to reinforce reliability included use of the EUROTRACS database, which has a large sample size and includes patients from different countries and hospitals, and the application of robust statistical methods such as PS matching and a number of sensitivity analyses. In particular, survival bias was assessed by a sensitivity analysis excluding hospital stays <2 days. This analysis yielded results similar to the main analysis. A limitation in assessing outcomes in elderly ACS patients after PCI is the lack of information on bleeding. Although we could not examine bleeding events in our study, a recent clinical trial comparing an invasive and a conservative strategy in NSTEMI patients aged ≥80 years found no differences in bleeding complications [36]. Outcomes after PCI are also affected by time to PCI and by type of PCI, and they are interrelated, particularly in STEMI. In STEMI and in high-risk NSTEACS patients, the shorter the time to PPCI and invasive strategy the better the short- and long-term outcomes [41–47]. In addition, in STEMI patients, PPCI yields better outcomes than other revascularization and PCI types, although in specific settings primary and rescue PCI may be comparable [1,48]. Unfortunately, we did not have information on time to PCI and type of PCI, and it is possible that the inclusion of these two variables could have affected our results. Another potential limitation was the lack of frailty measures, as individuals with frailty have more cardiovascular disease and vice versa. However, frailty is highly correlated with variables included in the PS, such as age, renal impairment and Killip class [49], so we would not expect a significant change in the results if frailty measures were included. Finally, medications (such as antiplatelet agents, statins, beta-blockers and ACEIs/ARBs) and comorbidities other than CKD, DM, hypertension, and previous MI, for example

the Charlson comorbidity index, were not included in the analysis because these data were not available in the EUROTRACS database. A study analysing a large ACS registry found no significant changes in the effect of reperfusion or an invasive strategy when including the mentioned medications or a few comorbidities [31]. However, older adults can be prescribed with many other drugs which may cause high-risk events such as bleeding. In addition, elderly comorbidities include cognitive impairment, dementia, and disability which influence clinical decision making and may affect the results of this study [50].

4.2. Conclusion

Patients with MI who received a PCI during hospital admission had a lower risk of in-hospital mortality regardless of sex, age, presence of ST elevation, and DM or CKD. These results add up to the existing literature for patients younger than 75 years and provide robust evidence for the indication of PCI in elderly MI patients with DM and CKD presenting with or without ST elevation.

Conflict of interest

Dr. Tavazzi received personal fees from Servier, St Jude Medical, Cardiorentis, Boston Scientific, CVIE therapeutics, and Medtronic, unrelated to the submitted work. Dr. Ferrières received research grants from Amgen, Astra Zeneca, Genzyme, MSD and Servier, unrelated to the submitted work.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijcard.2017.07.054.

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