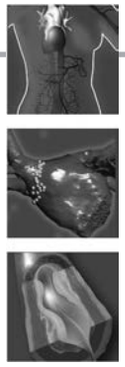

Impact of age on outcomes of percutaneous coronary intervention in acute coronary syndromes patients

Percutaneous coronary intervention (PCI) is a safe and effective procedure to reconstitute myocardial perfusion and has been demonstrated to improve prognosis in patients with acute coronary syndrome. With advancing age, PCI carries a higher risk for acute coronary and other vascular complications. Periprocedural mortality risk after PCI demonstrates a curvilinear relationship with age, with the highest mortality rates in the elderly. However, the magnitude of risk depends strongly on the presence and severity of additional clinical, angiographic and procedural factors. Among patients with acute coronary syndrome, the most meaningful mortality predictors are hemodynamic instability and acute ST elevation myocardial infarction. In addition, comorbidities such as renal insufficiency, diffuse and calcified coronary pathology and procedural complications increase the risk for death. Therefore, decision-making in interventional procedures is not solely dependent on the numerical age but mainly on additional factors. However, despite a higher rate of complications, PCI has been shown to improve clinical outcomes in the elderly with acute coronary syndrome.

KEYWORDS: acute coronary syndrome ■ age ■ mortality ■ percutaneous coronary intervention ■ prognosis

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Percutaneous coronary intervention (PCI) was introduced by Grüntzig in 1978 [1]. Since then, PCI has benefited from advances in technique, operator ability and adjunctive medical treatment that have made it possible to treat even severe coronary artery disease and complex lesions in unstable clinical situations [2]. Acute coronary syndromes (ACS) are a major cause of cardiovascular morbidity and mortality [3]. PCI is the established reperfusion modality and has been demonstrated to improve prognosis in patients with ACS [4]. In addition to comorbidity, age is one of the major determinants of clinical outcome in patients with ACS [5]. An increasing number of elderly patients require interventional therapy. This is a challenge for modern cardiology since the elderly are at higher risk for complications compared with younger patients [6–11]. In the past, elderly cardiac patients, particularly those with severe comorbidities, have been underrepresented in randomized clinical trials relative to their disease prevalence [12]. Therefore, in this article, we evaluate age-related differences in outcomes of patients undergoing PCI for ACS. Furthermore, age-dependent effects on clinical characteristics, adjunctive medical treatment and procedural details are analyzed.

Coronary artery disease

Structural and functional changes of arteries are involved in the aging process. This includes luminal enlargement and calcification, as well as intimal and medial thickening. In addition, vascular stiffness increases and endothelial function declines with age [13,14]. The pathophysiology of ACS is different in the elderly compared with a younger cohort. The frequency of rupture/dissection is greater and culprit lesions contain more thrombus in younger patients. By contrast, in older patients, lesions are predominantly calcified with less positive remodeling (lesion/mean reference arterial area ≥1) [15]. Differential effects of pharmacology and mechanical interventions in the elderly may reflect differences in the underlying pathophysiology. Furthermore, coronary angiography usually reveals more severe coronary artery disease with advancing age. As the patient gets older the incidence of three-vessel and left main disease increases [16,17]. Interestingly, no major age-related differences in lesion characteristics can be observed. Complex stenoses, such as type C lesion, bifurcation or in-stent restenosis, do not appear to occur more often among the elderly [8].

Cardiac & noncardiac comorbidities

Many observational studies have demonstrated that the baseline risk profile for ACS increases with age. In comparison with younger patients, elderly ACS patients are more frequently female, more likely to have diabetes, hypertension, renal insufficiency and a history of atherothrombotic events or PCI/coronary artery bypass graft and congestive heart failure. Heart failure and

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cardiogenic shock also occur more frequently in the elderly. In fact, more than half of the patients aged 75 years or older develop either systolic or diastolic heart dysfunction with their ACS. All of these factors are independent determinants for worse *a priori* prognosis. Even though the elderly represent a very high-risk subgroup with a more unfavorable clinical outcome, they receive less aggressive medical and invasive therapy than younger patients with ACS [18–22].

Non-ST elevation acute coronary syndromes

The mean age of men and women with non-ST elevation ACS (NSTE-ACS) is significantly higher than that of those with ST elevation myocardial infarction (STEMI). Consequently, the elderly comprise an increasing proportion of patients with NSTE-ACS. In a contemporary Italian registry, over 35% of the patients were 75 years of age or older [23]. The benefit of an early invasive strategy appears to be age-dependent. In the Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy – Thrombolysis in Myocardial Infarction (TACTICS-TIMI) 18 trial, patients hospitalized with unstable angina and non-STEMI were randomly assigned to an early interventional or conservative ischemia-guided procedures. Among the elderly (75 years of age and older), the invasive management strategy conferred a significant reduction of nonfatal reinfarction and major adverse cardiac events at 6 months. In patients younger than 75 years of age, a significant reduction of cardiovascular events could not be observed. The occurrence of death tended to be lower in the elderly treated with an invasive strategy, but the difference was not significant [24]. Despite a potentially greater benefit, elderly patients receive invasive treatment less often than younger patients [6]. In an analysis of the Sibrafiban versus Aspirin to Yield Maximum Protection from Ischemic Heart Events Post-acute Coronary Syndromes (SYMPHONY) and the 2nd SYMPHONY trials, the elderly (≥75 years of age; n = 1794) with NSTE-ACS underwent cardiac catheterization less often than younger patients (<75 years of age; n = 14,043; 53 vs 63%; adjusted OR: 0.53 [0.46, 0.60]) [25].

ST elevation myocardial infarction

As previously noted, on average, patients with STEMI are younger than patients with NST-ACS. However, as these patients get older, they present less frequently with chest pain and prehospital delays are more prevalent [26]. One of the most important factors associated with failure to receive emergent PCI or fibrinolytics is age [27]. Advancing age is associated with worse outcomes, and the risks increase in proportion to age. The risk:benefit ratio favors primary PCI over fibrinolysis, regardless of age [28]. With advancing age, fibrinolytic therapy is associated with an increased risk for hemorrhagic stroke. In the Global Use of Strategies to Open Occluded Arteries in Acute Coronary Syndromes (GUSTO)-IIb angioplasty substudy, 1138 patients were randomized to receive primary PCI or fibrinolysis. For each 10-year patient group, outcome was improved with PCI compared with fibrinolysis. Irrespective of reperfusion therapy risk increased with age. After adjusting for confounders, each increment of 10 years of age increased the risk of death or myocardial infarction by 1.32-fold [29]. In the Senior Primary Angioplasty in Myocardial Infarction (PAMI) study, which examined patients older than or equal to 70 years of age, angioplasty was superior to fibrinolysis in reducing the combined secondary end points of death, disabling stroke or reinfarction in this high-risk patient population [30]. In a German observational study, a total of 2045 patients older than 75 years of age (median age: 80.1 years; 53.9% women) with acute STEMI were included. Of these, 51% were treated conservatively, 19% with fibrinolysis and 30% with primary PCI. Mortality rates in the elderly with STEMI are much worse than in younger patients. In-hospital mortality in the three groups was 23.4, 25.4 and 10.2%, respectively, while total mortality after 1 year was 52.4, 41.3 and 19.3%, respectively [24]. The recently presented Tratamiento del Infarcto Agudo de Miocardio en Ancianos (TRIANA) study compared fibrinolysis and primary PCI in patients older than 75 years of age with STEMI of less than 6 h duration [31]. The study was prematurely terminated after the first 266 patients because of slow recruitment. However, there was a trend towards a lower morality, reinfarction and stroke rate with primary PCI. This difference was not statistically significantly after 12 months (27.3 vs 32.1%). Elderly patients often have contraindications against fibrinolysis. Primary PCI reduces the incidence of stroke in elderly compared with fibrinolysis. Therefore, primary PCI should be regarded as the preferred reperfusion therapy in the elderly.

Procedural details

With increasing age, high-risk interventions become more prevalent. The elderly undergo multivessel PCI or interventions of left main

stem and bypass grafts more often than younger patients [16,17]. Nevertheless, procedural success rates are usually very high in young patients, but also in old and very old patients. However, data from observational studies have reported conflicting results on age-related differences in procedural success. Feldman and coworkers found slightly higher success rates in younger patients. Among those undergoing emergency PCI, angiographic success was 97.7% in the less than 60-year-old age group, 95.2% in the 60–80-year-old age group and 92.7% in the over 80-year-old age group [17]. In another study assessing interventional results by Kobayashi *et al.*, angiographic success was identical (99%) in patients under and over 80 years of age [8]. However, one has to take into consideration that only patients receiving stenting were enrolled and the percentage of emergency PCI was quite low.

Stenting rates are also very high among patients undergoing PCI for ACS, regardless of the patients' age [17]. In a recent publication by Douglas *et al.*, patients aged 65 years or older who were receiving drug-eluting stents (DES) had significantly better clinical outcomes than their counterparts treated with bare-metal stents [32]. However, age-related differences in the usage of bare-metal stents and DES could be seen. In the contemporary PCI registry of the Euro Heart Survey, elderly patients received DES less often in comparison with younger patients [33].

Adjunctive anti-thrombotic treatment

With advancing age, the percentage of patients with chronic oral anticoagulation and renal insufficiency dramatically increases [6–11]. Therefore, creatinine clearance should be calculated for all elderly patients to enable appropriate dosing [34]. There are insufficient data regarding adjunctive anti-thrombotic therapy in these high-risk patients [12]. Therefore, it is very difficult to make definitive recommendations on whether treatment in the elderly should differ from younger patients. Regardless of age, glycoprotein (GP) IIb/IIIa inhibitors are recommended in ACS patients undergoing PCI [35,36]. Previous observational studies have demonstrated that the use of GP IIb/IIIa inhibitors is significantly higher among younger patients [21]. In addition to aspirin, clopidogrel has shown that it improves prognosis in patients with ACS. Benefits are similar in all age groups [37]. However, in daily clinical practice the use of dual antiplatelet therapy is higher in younger patients [21]. Prasugrel – a novel thienopyridine – appears be a stronger and more stable antiplatelet agent than clopidogrel and is very effective in reducing ischemic events in patients undergoing PCI for ACS. However, its use does not appear to be more beneficial than clopidogrel in the elderly [38]. Bivalirudin monotherapy has been shown to reduce bleeding complications in patients compared with GP IIb/IIIa inhibitors and heparin in patients with NSTE-ACS and STEMI. This advantage was not associated with an increase in ischemic complications [39,40]. Therefore, bivalirudin appears to be an attractive alternative, especially in elderly patients. Clinicians' reluctance to use more aggressive anti-thrombotic treatment regimes in the elderly has been potentially justified by the higher risk of minor and major bleeding. Notwithstanding, dual antiplatelet therapy should not be withheld from elderly patients undergoing PCI for ACS.

Outcome

Age itself is a very powerful determinant for the clinical outcome in ACS patients after PCI [16,17,41,42]. Periprocedural mortality risk after PCI demonstrates a curvilinear relationship with age. Data from the contemporary PCI registry of the Euro Heart Survey demonstrate that after adjustment for confounding variables, the age group of 40–50 years of age has the lowest mortality rates (Figure 1) [31]. Interestingly, patients younger than 40 years have a slightly increased risk. At present, the reasons for this can only be speculated upon. It has been hypothesized that these patients suffer from a very aggressive atherosclerosis [37]. However, in the age group of 60–65 years of age, age is already a significant independent prognostic factor. After a further moderate increase in the age groups of 65–70 and 70–75 years of age, a precipitous rise was observed in patients older than or equal to 75 years of age. An age cut-off of older than or equal to 75 years of age constitutes an independent high-risk variable with a sixfold increased risk of in-hospital mortality. The incidence of in-hospital death is 5.7% among patients older than or equal to 75 years of age, in comparison with 1.9% among patients younger than 75 years. Considering the high-risk scenario of an ACS, these mortality rates are fairly low, most likely due to advances in PCI technique and operator ability, as well as adjunctive medical treatment. In addition, pathophysiological alterations

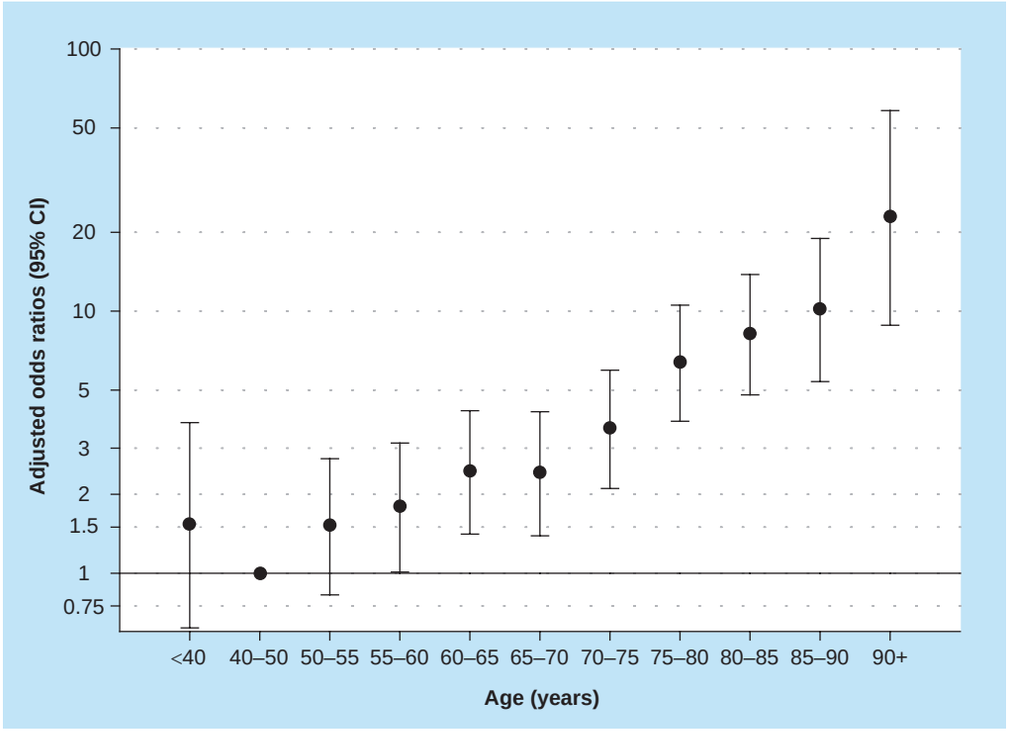

Figure 1. Odds ratios for age groups, adjusted for gender, diabetes, hemodynamic instability, STEMI, renal insufficiency and prior MI.
The 40–50 years old age group is the reference category.
MI: Myocardial infarction; STEMI: ST elevation myocardial infarction.

such as increasing calcification and deteriorating endothelial function, and the higher prevalence of cardiac and noncardiac diseases all contribute to the higher adverse event rates among the elderly undergoing PCI. The higher likelihood of death in elderly patients is partly attributed to more electric and mechanical complications. Shock occurs in more than 10% of STEMI patients older than 75 years of age and is a result of advanced left ventricular dysfunction or ventricular and papillar muscle rupture [43]. As previously stated, the incidence of heart failure and pulmonary edema is as high as 50% in patients over 80 years of age. This may be explained by diminished response to β-adrenergic stimulation, decreased vascular compliance and ventricular hypertrophy [44].

With advancing age, PCI carries a higher risk of acute coronary and other vascular complications. As stated previously, age is clearly an independent risk factor for periprocedural mortality. However, the magnitude of risk depends strongly on the presence and severity of additional clinical, angiographic and procedural factors. Batchelor and coworkers investigated the hospital course of octogenarians undergoing PCI [16]. As in younger patients, cardiogenic shock and acute STEMI are the strongest predictors of hospital death. Comorbidities such as history of stroke, congestive heart failure, chronic renal failure, peripheral artery disease and diabetes mellitus are also independent determinants of death in young and older patients [16,17,19]. Female gender might also be associated with an increased risk for adverse events [10]. This is of particular importance as the percentage of women with ACS is high among old and very old patients and increases yearly. Since women have smaller coronary vessels, it has been assumed that the worse outcomes are related to the mechanical factor of working within a smaller lumen diameter [45]. Moreover, the extent of coronary pathology determines the outcome in patients with ACS treated with PCI. The presence of left main disease, left anterior descending artery stenosis or three-vessel disease is associated with a higher mortality. As previously noted, coronary artery disease is more severe among the elderly [16,17]. In addition, lesion characteristics appear to play an important role; the presence of complex lesions such as type C is predictive of hospital death [46].

Age is also a major determinant for the occurrence of noncardiac complications. As the patients get older, the incidence of stroke,

major bleeding and renal failure requiring dialysis increases significantly [47]. Again, as well as age, cardiac and noncardiac comorbidities extensively contribute to an increased risk. However, there are ways to minimize the risk of PCI in the elderly. Radial instead of femoral access can reduce the risk of bleeding complications at the puncture site. Moreover, owing to the high prevalence of chronic renal insufficiency among the elderly, a biplane catheterization laboratory should be used to minimize the amount of contrast media.

In geriatric medicine, outcomes of particular relevance in this age group, such as quality of life, independence and physical function, should also be considered. In addition, the presence of dementia and frailty strongly influence treatment goals [33].

Future perspective

The percentage of elderly patients with comorbidities undergoing PCI for ACS increases annually. These patients are at a high risk for adverse events and mainly contribute to peri-interventional mortality. In particular, we do not have sufficient data regarding adjunctive medical treatment in this patient group. Randomized controlled trials that also enroll patients with renal insufficiency or chronic oral anticoagulation are warranted in order to define the optimal anti-thrombotic strategy and ultimately improve medical care in these patients. Furthermore, multicenter prospective registries documenting variables such as quality of life, physical function and mental impairment are important to reflect on the risks and benefits of interventional treatment in elderly patients in a real-world scenario.

Executive summary

Coronary artery disease

- Luminal enlargement, calcification, intimal and medial thickening and vascular stiffness increase, and endothelial function declines with age.
- Coronary angiography reveals more severe coronary artery disease with advancing age.

Cardiac & noncardiac comorbidities

- Baseline risk profile increases with age: there is more diabetes, hypertension, renal insufficiency, history of atherothrombotic events or percutaneous coronary intervention (PCI)/coronary artery bypass graft, congestive heart failure and cardiogenic shock.

Non-ST elevation acute coronary syndromes

- As the mean age is higher than in ST elevation myocardial infarction (STEMI), the elderly comprise an increasing proportion of patients with non-ST elevation acute coronary syndromes (ACS).
- The elderly possibly show a greater benefit for an early invasive strategy than younger patients.
- The elderly receive invasive treatment less frequently.

ST elevation myocardial infarction

- Patients with STEMI are younger than patients with non-ST elevation ACS.
- With advancing age, patients present more frequently with atypical symptoms and less often receive primary PCI.
- Although primary PCI improves outcomes over fibrinolysis, it does not appear to be more beneficial in older patients than in younger patients, but does reduce the rate of stroke substantially in the elderly.

Procedural details

- High-risk interventions become more prevalent with increasing age.
- Procedural success rates are very high in all age groups, with no major age-related differences.
- Coronary stenting rates are not different between younger and elderly patients.
- The elderly receive drug-eluting stents less often in comparison with younger patients.

Adjunctive anti-thrombotic treatment

- With advancing age it becomes difficult to make definitive recommendations regarding adjunctive antithrombotic treatment owing to comorbidities and insufficient data.
- The use of intense anti-thrombotic therapy with glycoprotein IIb/IIIa inhibitors and dual antiplatelet therapy decreases with increasing age.
- Bivalirudin monotherapy in comparison with glycoprotein IIb/IIIa inhibitors decreases bleeding complications, especially in the elderly.
- Prasugrel does not appear to be more beneficial than clopidogrel in elderly patients undergoing PCI for acute coronary syndromes.
- Dual antiplatelet therapy should not be withheld from elderly patients undergoing PCI for ACS.

Outcome

- Age itself is a very powerful determinant for clinical outcome in ACS patients after PCI.
- Periprocedural mortality risk after PCI demonstrates a curvilinear relationship with age.
- An age cut-off of patients older than or equal to 75 years of age constitutes an independent high-risk variable with manifold increased risk for pathophysiological alterations of the coronary vessels and, in addition, the higher prevalence of cardiac and noncardiac diseases contribute to higher adverse event rates with advancing age. Irrespective of age, cardiogenic shock and acute STEMI are the strongest predictors of death. Age is a major determinant for the occurrence of noncardiac complications despite the higher complication rate. PCI in the elderly with ACS improves the clinical outcome in geriatric medicine, although quality of life, independence and physical function should also be considered.

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