What's Age Got to do with it? A Review of Contemporary Revascularization in the Elderly

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Abstract: Currently a quarter of all patients treated with percutanous coronary intervention (PCI) are aged >75 years, with this proportion steadily growing. This subset of patients have a number of unique characteristics, such as a greater number of cardiovascular risk factors and frequently a larger burden of coronary artery disease, when compared to younger patients, therefore potentially deriving increased benefit from revascularization. Nonetheless this population are also more likely to experience procedural complications, secondary to age-related physiological alterations, increased frailty and increased prevalence of other co-morbidities. This article reviews the various aspects and data available to clinicians pertaining to and guiding revascularization in the elderly, including the use of adjuvant pharmacotherapy, specific considerations when considering age-related physiology, and revascularization in acute coronary syndromes.

Keywords: Elderly, revascularization, pathophysiology.

INTRODUCTION

The prevalence and proportion of elderly patients undergoing or being referred for coronary revascularization is increasing [1]. The elderly are routinely excluded in randomized clinical trials of cardiovascular disease and revascularization therapy in particular. This reduced representation in the medical literature has resulted in limited and frequently insufficient data to adequately guide treatment. Nonetheless cardiovascular disease remains the leading cause of morbidity and mortality amongst the elderly [2]. Whilst ACC/AHA guidelines state that age should not influence the decision about cardiac care, elderly patients have historically been less likely to receive coronary revascularisation [3, 4].

Interventional cardiologists were initially reluctant to perform revascularization procedures in the elderly because of the perceived comparative increased risk to reduced benefit obtained by revascularization in this subset of patients. However, there has been a paradigm shift in the treatment of this group of patients, with a quarter of all percutaneous coronary interventions (PCI) performed in patients aged ≥75 years and 12% performed in those aged ≥80 years [5, 6]. This review will address the growing use of PCI in the elderly, specifically examining the following aspects: the pathophysiological characteristics seen in elderly patients that place them at increased risk of adverse events; safety and efficacy of elective and acute-setting PCI; the role of coronary artery bypass grafting; and advances in adjuvant anti-platelet therapy.

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THE PATHOPHYSIOLOGY BEHIND AGE-ASSOCIATED PCI RISK

Coronary and Vascular Anatomical Alterations

Increasing age is directly related to coronary calcification, with CT imaging demonstrating a greater than 10% yearly increase in risk of a coronary calcium score >900 [7]. This increase in coronary medial calcification, in addition to the multi-vessel disease frequently present in elderly patients, necessitates more complex interventional strategies, resulting in an inherently higher procedural risk in this group. Specifically, intervention on heavily calcified plaques is associated with increased peri-procedural complications and decreased procedural success. This is predominantly because of inadequate lesion preparation, when adjunctive techniques such as rotational atherectomy are not utilized, and therefore inadequate stent expansion and deployment, resulting in a potential mechanical substrate for increased rates of restenosis and stent thrombosis [8-11] . Furthermore, increased coronary vessel tortousity is also evident in older patients, resulting in increased difficulty of balloon and stent deployment. These factors together with a greater risk of complications from vascular access, make PCI technically more challenging [12].

Haematological Alterations

Demonstration of the age-related changes in haemostasis may provide further insight into the possible factors that increase procedural and longer-term complications. Mari *et al.* proposed the hypercoaguability of older patients, caused by elevated levels of activated factors such as VII, IX and X, in addition to increased platelet reactivity, culminating in an increased risk of acute stent thrombosis [13-15] . However, this inherent increase in thrombosis risk is also countered by

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the increased risk of vascular bleeding complications, likely secondary to age-related hyper-fibrinolysis and thrombus instability [16-18].

Drug Metabolism

Elderly patients have a reduced lean body mass and increased adipose tissue compared to younger populations, resulting in heightened effects from drug therapies. Reduced liver mass and hepatic flow leads to a reduction in first pass metabolism and liver cytochrome P450 activity in the elderly. Moreover, as a consequence to age-dependent decline in renal function the use of anti-thrombotic medication such as low-molecular weight heparin and glycoprotein IIb/IIIa inhibitors, may lead to the increase in bleeding complications when used in the elderly [19].

Impaired Systemic and Coronary Haemodynamics

Advancing age results in a number of vascular and haemodynamic alterations that, in the presence of coronary artery disease, lead to a speedier progression along the ischaemic cascade because of reduced compensatory function. Vascular calcification and collagen cross-linking may play a role in the increased rigidity of systemic arteries, which causes a rise in systolic blood pressure, left ventricular afterload and therefore oxygen demand. In congruence with this alteration in vessel wall function, diastolic blood pressure is reduced, leading to a resting impairment in coronary and myocardial perfusion. In the presence of an obstructive epicardial stenosis there is an additional mismatch in myocardial oxygen 'supply and demand' [20]. Furthermore, the effectiveness of the usual inotropic and chronotropic compensatory mechanisms are reduced in elderly patients, due to impairment of beta-adrenergic-receptor function. In addition, sino-atrial node dysfunction attenuates the ability of the heart to adjust to fluctuations in systemic pressure [21, 22].

Increasing Co-Morbidities

There are a number of age-related co-morbid conditions that confer an adverse prognosis. Baseline renal dysfunction and increasing age are significant predictors of contrast-induced nephropathy following PCI [23].

An individual patient's 'frailty' has been defined as a syndrome including physical functional decline, malnourishment, cognitive impairment, and reduced physical capacity to stressors. Fried *et al.* suggest that the prevalence of frailty is upwards of 10% in populations aged between 75-85 years, and rises steeply to 25% in individuals over the age of 85 years [24]. Frailty is linked with increased morbidity and mortality and is an independent predictor of adverse outcomes, such as falls, infections, development of disability, and hospitalization [25].

Cultural Values

Whilst an elderly person may be able to physically withstand the procedure, certain cultural values have contributed to patients themselves refusing PCI despite their potential eligibility [26].

Safety and Effectiveness of Percutaneous Coronary Intervention (PCI) in the Elderly

There was a degree of caution in performing revascularization procedures in the elderly during the initial years of angioplasty. Data from the 1990's, suggest that post-PCI complications, including death, MI, stroke, renal failure and vascular complications, were 2-4 times more likely to occur in octogenarians than in a younger age groups [27]. Furthermore, it was clear that the presence of additional co-morbidities had a significant impact on outcome, with left ventricular dysfunction being the most predictive of adverse outcomes. Mortality was less than one percent for patients >80 years with no risk factors but reached 7.2% for patients >80 years with LVEF <35%. However further studies performed during the same era suggested a varying mortality rate of 8-20% for PCI in those aged 80 or above [28, 29].

As time progressed, development of revascularization protocols, with improvements in operator technique, guide-catheter and guide-wire technology combined with the use of evidence-based drug therapies, including, the use of dual anti-platelet, high-intensity statin therapy, and glycoprotein IIb/IIIa inhibitors, were adopted [30]. These changes led to reduced mortality figures with Singh *et al.* highlighting this in the National Cardiovascular Disease Registry (NCDR) CathPCI Registry evaluating trends in mortality post-PCI across the USA in the early 2000s, showing the overall mortality was much improved compared to previous observational studies, being 1.2% in this large all-comer study. Most pointedly, from 2001 to 2006, whilst a decline in mortality was observed across all age ranges, the decline in mortality was greatest in the oldest patient group, emphasizing the improvements made to PCI technique and adjunctive management [31].

Acute Coronary Syndrome PCI

ST-elevation Myocardial Infarction

In recent ACCF/AHA guidelines for the management of myocardial infarction with ST-segment elevation, numerous priorities for implementation were recognized, including the need to immediately assess the patient's eligibility for PCI, irrespective of age, ethnicity or sex [32]. Whilst PCI is the gold-standard treatment for ST-elevation MI, patients >75 years were under represented in major randomized PCI trials.

Observational studies, in the pre-PCI era, had shown that thrombolysis for STEMI may not be beneficial to elderly patients. Thiemann *et al.* demonstrated that for patients aged 76-86, receiving thrombolysis for STEMI was associated with a 38% increase in 30-day mortality [33], with increased bleeding counteracting the anti-ischaemic properties afforded by thrombolysis. Furthermore, subsequent observational studies comparing PCI to thrombolysis in the elderly were encouraging. Mehta *et al's* Global Registry of Acute Coronary Events (GRACE) registry compared primary PCI to thrombolytic therapy in elderly patients with acute myocardial infarction, which showed primary PCI was found to be associated with a strong signal toward reduced in-hospital re-infarction and mortality and cardiogenic shock (Fig. **1**), with no difference bleeding or stroke across all age groups [34] (Table **1**).

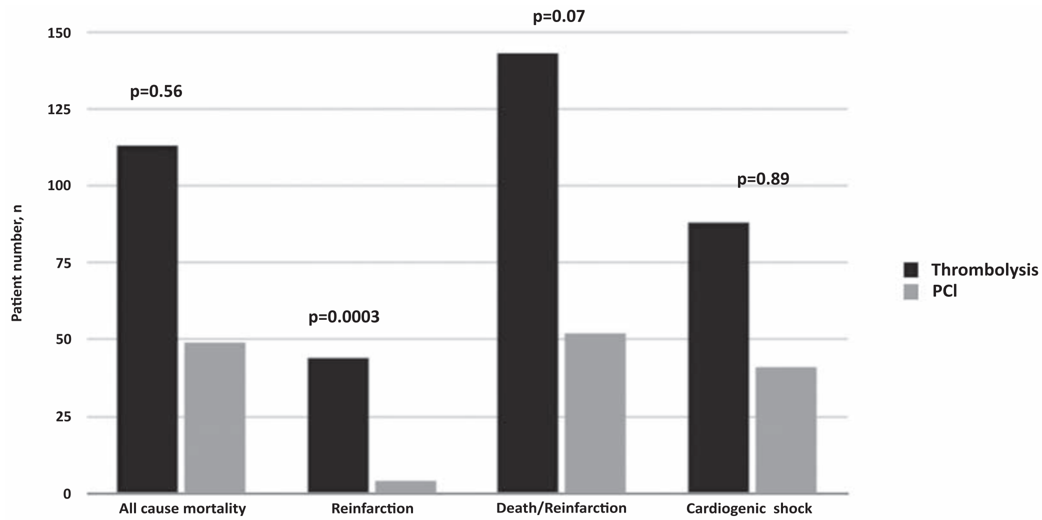

Fig. (1). In-hospital End-points for all-cause mortality, re-infarction, death and re-infarction and cardiogenic shock (Adapted from Mehta *et al.* [34]).

Despite observational studies suggesting the potential benefit with PCI, no randomized control trials (RCTs) had been performed in this high-risk elderly population. However latterly this has been addressed with a number of trials assessing PCI in the setting of ACS. The largest randomized control trial involving treatment options for elderly patients with STEMI was the Senior Primary Angioplasty in Myocardial Infarction (Senior PAMI) study, which enrolled 483 patients, aged greater than 70 years presenting with STEMI, with patients randomized to PCI or fibrinolytic therapy. Amongst patients aged 70-80 years, there was a 38% reduction in death and a 55% reduction in combined endpoints of death, CVA and re-infarction. However, amongst the very elderly, in patients over 80 years, no difference between PCI and fibrinolysis was observed [35]. Further to this a large European RCT compared PCI to fibronlysis [36]. Bueno *et al.* randomized 266 elderly patients >75 years to PCI or fibrinolysis, with a mean age of 81 years. Those randomized to the PCI-arm experienced lower rates of death (13.6% vs. 17.2%, p=0.43), re-infarction (5.3% vs 8.2%, p=0.35) and stroke (0.8% vs 3%, p=0.18). The conclusion here was that there was a signal that primary PCI seemed to be the better reperfusion therapy for STEMI in elderly patients.

To further delineate outcomes in very elderly patients undergoing PCI, a recent registry examined nonagenarian patients undergoing PCI following acute myocardial infarction. Despite the trend to group all patients older than 80 as 'very elderly', data now exists (from the CRUSADE registry) that nonagenarians have different clinical characteristics than octogenarians, including reduced previous cardiac disease, reduced cardiac risk factors and high prevalence of female gender [37]. A further retrospective registry study evaluated nonagenarians presenting with STEMI and treated within twelve hours of presentation [38]. The study was small, randomizing only 27 patients between 2003 and 2011, with 19% (n=5) patients dying during their index hospitalization. Six-month follow-up revealed a survival rate of 67% (n=18), suggesting that there remained a benefit to performing PCI, where suitable, in this very elderly population.

Observational studies looking at the uptake of PPCI to treat elderly patients with ACS suggest the interventional community are changing their practice in accordance with the growing evidence in this subset of patients and treating more elderly people with percutaneous revascularization. Khera *et al.* used the United States Nationwide Inpatient Sample to examine temporal trends in PCI uptake from 2001-2010 [39]. Patients were divided into age groups: 65-79 and >80 years. The use of PCI for STEMI increased 33.5% and 22% in each group respectively. A decreased in-hospital mortality was also seen in the >80 age group (150 per 1000), which was apparent in the 65-79 age group (115 per 1000), suggesting the greatest benefit of PPCI is when it is performed in the elderly population when compared with other age groups. Additionally, PPCI is not only is it useful in terms of preventing death, but specifically in the elderly, it brings about most improvement in physical health at 6 months when compared to younger people [40].

Non-ST Elevation Myocardial Infarction

In excess of a third of all patients admitted with a non-ST-elevation myocardial infarction (NSTEMI) are greater than seventy-five years of age [41]. This population represents a higher-risk cohort, for the age-related pathophysiological reasons outlined above. They are more vulnerable to having more extensive coronary artery disease and increased co-morbidities, whilst discordantly being much less likely to receive early invasive strategies. Liistro *et al.* examined outcomes of patients presenting with NSTEMI undergoing revascularization (CABG or PCI), and found that death (3.1% vs 0.3%, p=0.02) and death plus non-fatal myocardial infarction (5.6% vs 1%, p=0.01) were significantly more common amongst those aged >75 years, when compared to a younger cohort (<75 years). However, percutaneous revascularization in the elderly population led to a comparable 30-day all-cause mortality (1.9% vs 0%, p=0.1) and medium term (mean duration 10.7 months) cardiac mortality (2.9% vs 1.1%, p<0.01) [42].

In a study by De Servi *et al.*, an aggressive treatment strategy (involving angiography within 4 days, followed by revascularisation where possible) was followed in 39% >75 years and 56% in the <75years group (p=<0.001) [43]. At 30-days following NSTEMI, revascularization had been performed in 30% of patients in the older group and 48% in the younger group (p=<0.001). In-hospital 30-day mortality rates were almost four times as high in the older group, with adoption of a conservative strategy being an independent predictor of adverse outcome (OR 2.31), highlighting the importance of revascularization in this high-risk cohort in modifying and optimizing outcome. In addition the GRACE registry assessed outcomes in patients across all ages who underwent revascularization following NSTEMI. This reaffirmed the improved outcome with revascularization, with a significant reduction in 6-month mortality demonstrated in all age ranges: under 70 years (OR 0.52, 95% CI 0.37-0.72), 70-80 years (0.38, 0.26-0.54) and over 80 years (0.68, 0.49-0.95) [44].

Appropriate patient selection in the setting of elderly patients presenting with an ACS is an important determinant in both procedural and patient outcome. In order to help evaluate the risk of PCI to elderly patients presenting with ACS, Scherff *et al.* refined the SYNTAX score to help predict clinical outcomes. The original SYNTAX score (Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery) was developed to quantify coronary lesions with respect to their number, location and complexity. By incorporating clinical variables into that score, including age, creatinine and LVEF, a 'clinical SYNTAX' score can be calculated. This has been shown to predict 30-day mortality in patients with ACS undergoing PCI and is a valuable tool when risk-assessing patients, with age included as a variable, identifying those patients that are at increased risk of short term mortality and allowing a more informed decision to be made by the patient [45].

Elective PCI

Investigators of the *Trial of Invasive versus Medical therapy in Elderly* – (TIME) study evaluated treatment options in patients with chronic symptomatic coronary artery disease already on two anti-anginal drugs (Fig. **2**) [46]. All enrolled patients were aged over 75 years, and randomized to angiography ± revascularization or medical therapy. Whilst symptoms and quality of life improved in both groups, major adverse cardiac events were significantly reduced in the PCI treated cohort (19% vs. 49%, p=0.0001) (Fig. **3**). Furthermore, when PCI is compared to CABG in the setting of stable CAD, meta-analysis data has shown that PCI is associated with a reduced 30-day mortality (5.4% [95% CI 4.4-6.6%] vs 7.2% [95% CI 6.3-8.2%]), with equivalent rates of 1-year survival (87% [95% CI 84-91%] vs. 86% [95% CI 83-88%]) [47]. With the inference that, adoption of a percutaneous revascularization strategy, in the presence of failed medical therapy, leads to acceptable short and medium term outcomes in comparison with CABG, in the context of stable angina.

Despite the above studies and the fact that the procedure itself is deemed to be relatively safe for stable patients [48], even for those >90 years, some studies suggested that the prognostic benefit of PCI in stable disease may be limited [49]. Boden *et al.* randomized 2287 patients in the COURAGE trial, who had symptoms of angina [50]. 1149 patients underwent PCI with optimal medical therapy and 1138 received optimal medical therapy alone. Death, myocardial infarction and stroke showed no difference between the two groups, even though the patients in the PCI arm reported a symptomatic improvement. However, the major limitation with this trial was the exclusion of patients with high-grades of angina(> CCS class 3), in whom the degree of ischaemia would be greatest and therefore revascularization would afford the greatest benefit. Additionally, there was a substantial cross over from the medically treated arm to the revascularization arm, further diluting the power of the study. A substudy of COURAGE reaffirmed the hypothesis that revascularization in the presence of moderate to large amounts of ischaemic myocardium portends an improved outcome [51]. A meta-analysis performed by Trikalinos *et al.* in patients who had not systematically undergone ischaemia testing prior to risk stratification and PCI, demonstrated a similar

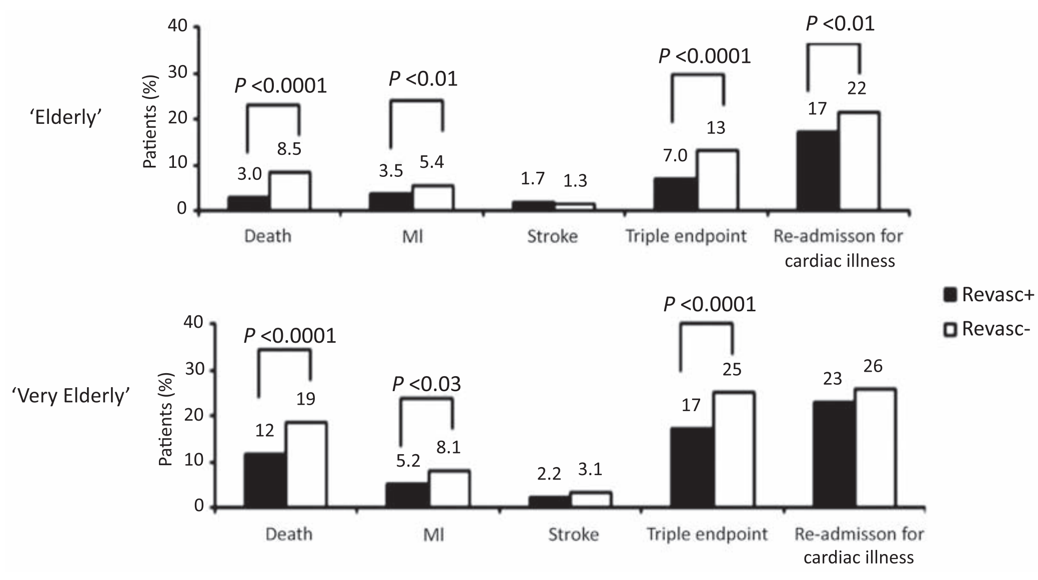

Fig. (2). Improved outcomes in both 'elderly' and 'very elderly' groups undergoing percutaneous revascularization from the GRACE registry of Acute Coronary Events. Devlin *et al.* [44].

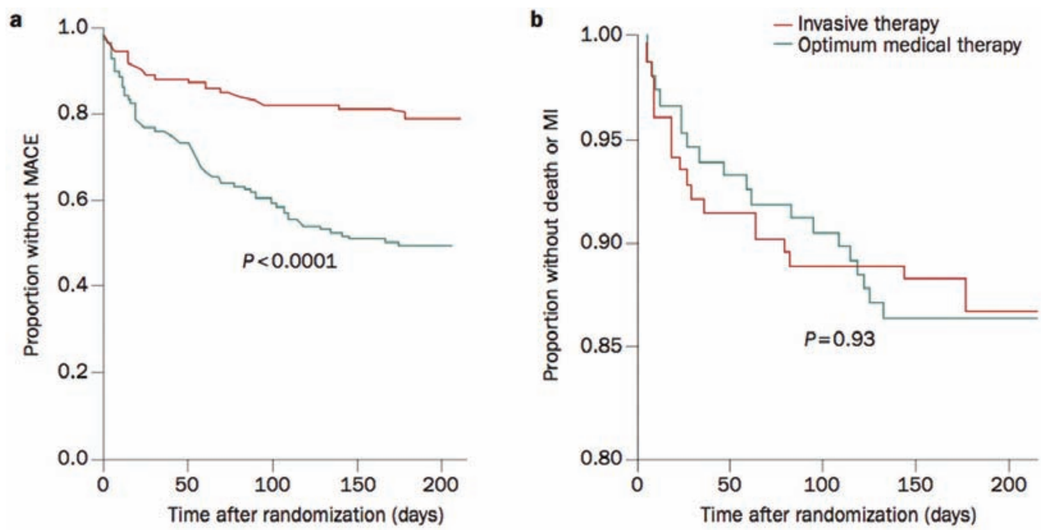

Fig. (3). Outcomes associated with invasive and optimum medical therapy for coronary artery disease among patients aged >75 years. a Event-free survival. B. Time to death or nonfatal MI. Abbreviations: MACE, major adverse cardiac event (death, recurrent MI, or rehospitalization for acute coronary syndromes); MI, myocardial infarction. Reprinted from *The Lancet*, 358, TIME Investigators, Trial of invasive versus medical therapy in elderly patients with chronic symptomatic coronary-artery disease (TIME): a randomised trial, 951–957, © 2001. [47].

trend, with medical therapy being the first-line treatment strategy in the presence low-grade stable angina [52]. However the importance of ischaemia-guided revascularization remains a safe and feasible option for all age groups in those patients that have failed a trial of medical therapy.

SPECIFIC CONSIDERATIONS IN THE ELDERLY

Anti-platelet Therapy

The initial approach and mainstay of ACS treatment is anti-thrombotic pharmaco-therapy. The combination of aspirin, clopidogrel and heparin, has led to a significant reduction in morbidity and mortality [53]. Additionally, platelet glycoprotein IIb/IIIa receptor antagonists used adjunctively during PCI, for both stable coronary artery disease [54] and in the ACS setting, have further reduced the incidence of death and MI, but at added cost of increased bleeding [55]. The excess in bleeding with more potent pharmotherapy is further heightened in the elderly population; therefore more judicious use of these drugs is required with consideration on an individual basis.

Clopidogrel improves outcomes when used for elective or emergency PCI [56]. Despite a significant bleeding risk, it remains the mainstay of anti-platelet treatment in patients undergoing percutaneous revascularization [57]. However, as clopidogrel has been shown to have a variable anti-platelet response and delayed onset of action, more stable and potent compounds have been sought [58]. Latterly, in the PLATO study, ticagrelor, a reversibly binding oral P2Y12-inhibitor, and clopidogrel were assessed [59]. In the sub-group of patients >75 years of age ticagrelor was associated with lower 12-month incidence of primary end-points (16.8% vs 18.3%, p=0.82). However, this anti-ischaemic effect came at a cost of increased bleeding, with intra-cerebral haemorrhage reported in ten times as many cases.

Prasugrel, a third generation thienopyridine has been shown to be markedly more potent than clopidogrel in inhibiting platelet function *in vivo* [60]. Clopidogrel and prasugrel were directly compared in acute coronary syndromes in the TRITON-TIMI trial. Whilst prasugrel was associated with lower rates of myocardial infarction, urgent target-vessel revascularization and stent thrombosis, it was associated with increased incidence of major bleeding in patients > 75 years [61]. The GENERATIONS trial compared prasugrel in 5mg and 10mg preparations with the more widely used clopidogrel 75mg, in stable coronary artery disease, in patients >75 years [62]. The pharmacodynamic response was more stable in the prasugrel-treated patients, with maximum platelet aggregation being reduced in these patients, when compared to clopidogrel and no different between the two dose regimens of the prasugrel arm. Whilst there was an increase in minor bleeding in the higher dose of prasugrel, those taking 5mg had similar minor bleeding rates to those on clopidogrel. Whilst major bleeding was not assessed this data provides a signal that prasgurel used in the lower dose may provide a more potent alternative anti-platelet in the elderly population.

In regard to GPIIb/IIIa inhibitor therapy, Kimmelstiel *et al.* demonstrated that elderly patients may have platelets that are more sensitive to GPIIb/IIIa inhibitor therapy than younger patients [63], and that may adversely alter the pharmacodynamics in this group, thereby increasing bleeding risk further. The use of GPIIb/IIIa's has reduced over time, though it continues to be used in certain high-risk scenarios, such as when a high degree of thrombus burden is evident angiographically, with the decision to administer the drug continuing to be done so on a case-by-case basis.

MULTIVESSEL AND COMPLEX REVASCULARIZATION

Mode of Revascularization: CABG or PCI?

Weintraub *et al.* recently reported from the ASCERT study (the ACCF and STS Database Collaboration on the

Comparative Effectiveness of Revascularisation Strategies) that in elderly patients with two-vessel or three-vessel stable coronary artery disease, there was no significant difference in 1-year mortality between the two resvascularization modalities (6.2% CABG vs. 6.5% PCI, RR 0.95, CI 95% 0.9-1.0) but at long-term (4 year follow-up), a lower mortality was observed in the CABG group (16.4% vs 20.8% respectively, RR 0.79, CI 95% 0.76-0.82) [64].

For octogenarians, McKellar *et al.* performed an extensive meta-analysis of 66 data-sets including in excess of 65,000 patients. Pooled mortality estimates for CABG and PCI groups were calculated showing that mortality was 7.3% (6.3%-8.2%) in the CABG group and 5.4% (4.4%-6.4%) in the PCI cohort at 30-days. There was no significant difference in one-year survival with either mode of revascularization (86% (83-88%) CABG vs. 87% (84-91%) for PCI). At five years, survival was 68% for CABG and 62% for PCI [65]. This important analysis concluded that octogenarians can tolerate either form of coronary revascularization procedure well. Whilst CABG may be associated with a higher mortality at 30-days, long-term survival figures are similar. It must be noted that comparisons of PCI and CABG are difficult, and selection bias will be present in the observational studies included in meta-analysis data. Percutneaous revascularization is likely to be the chosen mode of revascularization in a higher risk population with a greater number of co-morbidities, presenting with acute coronary syndromes and where haemodynamic compromise is evident.

Left Main Stem Revascularization

Left main stem disease has historically been revascularized with CABG as the primary modality over PCI [66]. However, there is a growing trend to treat LMS disease with PCI in view of a growing body of data which suggests that LMS-PCI is associated with similar MACE (major adverse cardiac events) rates as CABG [67]. Capodanno *et al.* presented a meta-analysis comparing the effectiveness of PCI with a drug-eluting stent (DES) platform versus CABG for LMS disease, stratifying risk according to age [68]. In patients greater than 75 years of age no difference in MACE was noted between those treated with either modality (PCI 16.4% vs CABG 13.9%, p=0.65), suggesting that in selected patients a PCI strategy to treat LMS disease was feasible and had good clinical outcomes.

Chronic Total Occlusions (CTO) Revascularization

A multinational CTO Registry including data from the US, Italy and South Korea provides some data on CTO intervention in a cohort of 213 patients aged >75 years [69]. After 5 years there were no differences in terms of procedural success, MI rates or mortality in the when comparing elderly versus younger patients. Reduced MACE (all-cause mortality, MI and need for CABG) were demonstrated in both groups, mostly driven by the reduced need for CABG at 5-years. Diabetes mellitus was observed to be an independent adverse predictor of MACE in elderly patients undergoing CTO interventions. The length of the CTO correlated with procedural success, with the highest likelihood of success in the elderly being when the lesion was less than 21mm. Accordingly current ACC/AHA guidelines for PCI indicate that percutaneous revascularization for CTO is a reasonable treatment option in patients with stable CHD if clinically and anatomically feasible irrespective of the patients age and carries a class IIa, level of evidence B [70].

Drug Eluting Versus Bare-Metal Stent Technology

The stenting technology and platforms used in contemporary percutaneous revascularization have undergone various RCTs which have been used to compare differences in outcomes between both, bare metal and drug-eluting, platforms. However elderly patients are routinely excluded from these analyses. Whilst it is hypothesised that DES platforms would confer reduced long term re-stenosis rates in the elderly when compared to bare-metal stents, it had not been definitely delineated. Elderly patients often have complex cardiac disease warranting the use of DES but have a higher risk of bleeding due to dual-antiplatelet therapy and the physical effects of ageing [71]. Groeneveld *et al.* compared DES and BMS in a cohort of elderly patients with stable angina. DES group was associated with a mortality hazard ratio of 0.83 compared to BMS, as well as lower rates of revascularization procedures in the subsequent 2 years [72]. Latterly, the XIMA (Xience or Vision Stents for the Management of Angina in the Elderly) study compared DES to BMS in octogenarian patients requiring angioplasty for stable angina [71]. 800 patients were randomized in this contemporary trial of PCI in the elderly. Both BMS and DES were associated with similar rates of all-cause death (7.2% vs 8.5%, p=0.50), stroke (1.2% vs 1.5%, p=0.77) and major haemorrhage (1.7% vs 2.3%, p=0.61). Whilst DES was associated with lower rates of myocardial infarction and target vessel revascularization, it was noted that there was a higher rate of non-cardiac death, with uncertainty raised over whether bleeding was considered a cause of non-cardiac death, with the incidence of major haemorrhage being concordantly increased in DES group [73].

However, an observational study further evaluated use of DES in elderly patients [74]. Data included all PCI patients >65 years undergoing inpatient stenting, encapsulating a study population of 262,700 patients. MACE rates were assessed at thirty months post-procedure, showing that overall mortality was greater in the BMS group compared to the DES group (16.5% versus 13.5%, p<0.001), as was incidence of MI (10% versus 7.3%, p<0.001). There were no significant differences in revascularization, stroke and major bleeding. The overall conclusion that DES are safe in patients aged >85 years. The current evidence therefore suggests that routine use of drug-eluting stents is safe and confers similar benefits to when used in younger patients.

Trans-radial vs. Trans-femoral Access

Achenbach *et al.* compared trans-radial and trans-femoral approach in elderly patients and showed that, whilst total fluroscopic screening time was longer for transradial compared to transfemoral (18.1 vs 15 mins, p=0.009), major complications (bleeding requiring surgery or transfusion and stroke) were reduced with a transradial approach (0% vs 3.2%, p<0.001) [75]. He *et al.*have subsequently conducted a meta-analysis to explore the issue further [76], where over two thousand patients from eleven studies were included in

Table 1. Summary of Key Trials in Revascularization of the Elderly.

Author	Year	Clinical syndrome & Age range	n	Study type	Outcome
Mehta RH, *et al.* [34]	2004	STEMI >70y	1,134	Observational	Primary PCI = lower rates of re-infarction (odds ratio [OR], 0.15; 95% CI, 0.05-0.44) and mortality (OR, 0.62; 95% CI, 0.39-0.96)
Bueno H *et al.* [36]	2011	STEMI >75y	266	RCT	The primary endpoint (all-cause mortality, re-infarction, or disabling stroke at 30 days) pPCI group (18.9%) versus 34 (25.4%) in the fibrinolysis arm; [OR, 0.69; 95% CI 0.38-1.23; P = 0.21].
Rigattieri S *et al.* [38]	2013	STEMI >90y	27	Observational	Procedural success 89%, defined as TIMI flow grade ≥ 2 and residual stenosis <20%. In-Hospital mortality 18.5%. Overall 6-month survival rate, 67%.
Liistro F *et al.* [42]	2005	NSTEMI All ages	159	Observational	Revascularization with CABG or PCI. Significant difference in cardiac death in the >75 yrs versus <75 yrs treated by CABG (19.3% vs 4.9%; p=0.05) compared to PCI (2.9% vs 1.1%; p=0.3) at 10 months FU.
Devlin G *et al.* [44]	2008	NSTEMI All ages	7,938	Observational	PCI was associated with reductions in 6-month mortality OR 0.38, CI 0.26-0.54 in elderly; 0.68, 0.49-0.95 in very elderly).
TIME Investigators. [46]	2001	Stable angina >75y	305	RCT	PCI led to reduced anginal burden and improved QOL. MACE occurred in 49% vs. 19% (p<0.0001) of patients in the conservative and invasive groups, respectively
Boden WE *et al.* [50]	2007	Stable angina All ages	2287	RCT	>4-year cumulative primary-event rates were 19.0% in the PCI group and 18.5% in the medical-therapy group (HR for PCI group, 1.05; 95% CI, 0.87 to 1.27; P=0.62).
De Belder A *et al.* [71]	2014	Stable angina >80y	800	RCT	No difference in primary endpoint (1-year composite of death, MI, CVA, TVR, or major haemorrhage) with BMS (18.7%) or DES (14.3%) (p = 0.09).
Capodanno D *et al.* [67]	2012	LMS disease (Stable and ACS) All ages	1,611	Meta-analysis	Meta-analysis showing no difference in 1-year MACE in those aged ≥75 years (16.4% vs 13.9%, p = 0.65).

the data analysis. Incidence of vascular complications (OR 0.25, CI 0.14-0.46) and major bleeding events (OR 0.31, CI 0.45-1.3) were reduced in trans-radial group and the average length of hospital stay was shorter. There was no difference in rates of MACE but the investigators found higher procedural success rate with the trans-radial route (OR 1.86, CI: 1.18-2.94). The authors' conclusions based on the meta-analysis was that the trans-radial route should be recommended as routine practice for elderly patients undergoing PCI, where feasible.

CONCLUSIONS

The increasing prevalence of revascularization in the elderly has sharpened the focus on methods of optimisation on PCI in this population. A number of factors play a role in this sub-set of patients including age-associated pathophysiological changes and increased co-morbid conditions making the elderly a high-risk group in terms of mortality and adverse events following percuteanous revascularization. However, despite the high-risk intrinsic nature of this population, coronary artery disease treated by PCI is likely to afford improvements in clinical outcomes and functional status. The decision when to perform revascularization is complex, and should consider the patient on an individual basis, with clarification of the goals of the therapy and the relative risks and benefits of performing the procedure. To further optimise outcomes, all modifiable risks, such as bleeding and PCI strategy with individualised access considerations, with trans-radial used where possible with appropriate lesion preparation with rotational atherectomy, and adjuvant drug use and dosing should be considered. Percutaneous revascularization in this cohort is unique in many respects and further research in reducing the current gaps in our knowledge is required and will lead to specific advances in PCI technique and pharmacotherapy, to enable further improvement in outcomes.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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