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REVIEW ARTICLE

Should Percutaneous Coronary Intervention be the Standard Treatment Strategy for Significant Coronary Artery Disease in all Octogenarians?

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Abstract: Coronary artery disease (CAD) remains the leading cause of cardiovascular death in octogenarians. This group of patients represents nearly a fifth of all patients treated with percutaneous coronary intervention (PCI) in real-world practice. Octogenarians have multiple risk factors for CAD and often greater myocardial ischemia than younger counterparts, with a potential of an increased benefit from myocardial revascularization. Despite this, octogenarians are routinely under-treated and belittled in clinical trials. Age does make a difference to PCI outcomes in older people, but it is never the sole arbiter of any clinical decision, whether in relation to the heart or any other aspect of health. The decision when to perform revascularization in elderly patients and especially in octogenarians 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. In ST-segment elevation myocardial infarction (MI), there is no upper age limit regarding urgent reperfusion and primary PCI must be the standard of care. In non-ST-segment elevation acute coronary syndromes, a strict conservative strategy must be avoided; whereas the use of a routine invasive strategy may reduce the occurrence of MI and the need for revascularization at follow-up, with no established benefit in terms of mortality. In stable CAD patients, invasive therapy on top of optimal medical therapy seems better in symptom relief and quality of life. This review summarizes the available data on percutaneous revascularization in the elderly patients and particularly in octogenarians, including practical considerations on PCI risk secondary to ageing physiology. We also analyse technical difficulties met when considering PCI in this cohort and the ongoing need for further studies to ameliorate risk stratification and eventually outcomes in these challenging patients.

Keywords: Octogenarians, acute coronary syndromes, chronic coronary syndromes, percutaneous coronary intervention, frailty, quality of life.

1. INTRODUCTION

"Elderly" applies to those people who are ≥65 years old, while those from 65 through 74 years old are defined as "early elderly" and those ≥75 years old as "late elderly." Octogenarian is a person who is between 80 and 89 years old. The proportion of octogenarians undergoing percutaneous coronary intervention (PCI) is steadily growing [1]. Octogenarians are consistently under-represented in randomized controlled trials (RCTs) of revascularization therapy, resulting in scarce evidence to accurately tailor treatment in this challenging group of patients. Nonetheless, coronary artery disease (CAD) remains the leading cause of death amongst octogenarians [2]. Whilst age itself should not influence clinical practice [3-5], historically, invasive therapy has been under-utilised in octogenarians, despite its proven benefit from revascularization [6]. However, there has been a paradigm shift in the treatment of this group of patients, with a quarter of all PCIs now being performed in the late elderly patients, and nearly 12% performed in those aged ≥80 years [7-9].

This review article summarizes the available data on percutaneous revascularization in the elderly patients and specifically in octogenarians, including practical considerations on PCI risk secondary to ageing physiology. We also analyse technical difficulties met when considering PCI in this co-

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hort and the ongoing need for further studies to ameliorate risk stratification and eventually outcomes in these challenging patients.

2. RISK OF PERCUTANEOUS CORONARY INTERVENTION SECONDARY TO AGE-RELATED PATHOPHYSIOLOGY (TABLE 1)

2.1. Anatomical Coronary Complexity

Increasing age is related to coronary calcification [10]. In a British study [9], 46% of the octogenarians undergoing PCI had calcified lesions, 20% tortuous anatomy, 20% multi--vessel disease (MVD), and 9% left main stem (LMS) stenosis [9]. The increment in coronary calcification, as well as the lesion complexity, necessitates the use of more complex interventional strategies with the employment of several auxiliary PCI kits [11], like cutting, scoring, super-high pressure non-compliant [12] and lithotripsy balloons [13], special microcatheters [14], atherectomy devices [15-17] resulting in an actually greater peri-operative risk in this group.

2.2. Peripheral Vascular Disease

The prevalence of peripheral vascular disease increases with age and has been shown to be an independent predictor of in-hospital mortality and adverse events post-PCI [18, 19]. While transradial approach has been widely reported to be safer than transfemoral in cardiac catherization [20], old age is one of the predictors for transradial approach failure [21]. The use of left radial access can reduce failure rates due to lesser subclavian artery tortuosity [22-24] and is associated with a reduction in fluoroscopy time and the number of catheters used [25].

2.3. Haematological Factors

Octogenarians are susceptible to both thromboembolic and bleeding complications. The hypercoagulability of older patients [26] and the documented increased risk of stent thrombosis (ST) [27, 28] are caused by a shift towards increased clotting and decreased fibrinolysis [26], increased platelet reactivity [29] and 'inflammaging' [30].

On the other hand, unpredictable pharmacokinetic and pharmacodynamic responses, polypharmacy (especially of antiplatelet and anticoagulant agents), drug interactions, and increased comorbidities, contribute to an increased risk of bleeding [31]. Moreover, because of age-dependent decline in renal function, the use of Non-vitamin K antagonist oral anticoagulants (NOACs) [32] and parenteral anti-thrombotic agents, such as low-molecular weight heparins, fondaparinux, bivalirudin and glycoprotein IIb/IIIa inhibitors (predominantly eptifibatide and tirofiban), may result in an increase in bleeding complications [33], thus dose modification is often needed [34].

2.4. Drug Metabolism

Octogenarians have a reduced enzyme induction capacity and are less able to tolerate an overdose of a drug [35-37].

2.5. Multiple Co-Morbidities

Octogenarians have an age-related worsening of vision, hearing, mobility, renal and cerebral function [38-41], and therefore may present with a higher risk of drug non-adherence [42, 43] leading to frequent hospital and physician visits, and significantly increasing health care costs [44].

2.6. Frailty

Frailty has been defined as a state of increased vulnerability [45] and its prevalence rises to 25% in octogenarians [46]. Several scoring systems have been created to quantify frailty and its impact on cardiovascular outcomes and what treatment strategies (conservative *vs* invasive) should be offered [47, 48]. Frailty scores are higher in women than men [49], rise steeply with increasing age [50] and vary according to the type of coronary therapy (*i.e.*, coronary artery bypass graft surgery [CABG], PCI, or optimal medical therapy only [OMT]) patients receive [51]. Freiheit *et al*. studied 374 patients undergoing elective coronary angiography (CA) followed by treatment (128 CABG, 150 PCI, 96 OMT) and observed for 30 months. A frailty index (FI) score was calculated at baseline and 6, 12, and 30 months after treatment. In late elderly patients, FI scores increased at baseline for CABG and OMT only and after 6 months for PCI patients. The participants who underwent CABG as their initial treatment trended toward higher mean FI scores at each follow-up than those who underwent PCI or received OMT only ($p=0.053$). U-shaped curves were observed for both PCI and CABG groups, but not to those assigned to OMT [51]. Damluji *et al*. estimated the prevalence of frailty among late elderly patients admitted with acute myocardial infarction (AMI) and examined the relationship between frailty, interventions, and mortality. From 2000 to 2016 in the United States, 469390 late elderly patients admitted with AMI. The median age was 82 years, 53% were women, and 75% were white. The prevalence of frailty was 19%. Frail patients were less likely to receive PCI than non-frail (15% *versus* 33%, $P<0.001$) and much less likely to receive CABG (1% *versus* 9%, $P<0.001$). Frailty was associated with higher mortality during AMI admission (unadjusted odds ratio [OR] 1.43, confidence interval [CI] 1.39-1.46). While there was a differential benefit of the interventions because of frailty, frail patients had reduced hospital mortality with PCI (frail: OR 0.59, CI 0.55-0.63; non-frail: OR 0.49, CI 0.47-0.50, P for interaction <0.001) and CABG (frail: OR 0.77, CI 0.65-0.93; non-frail: OR 0.74, CI 0.71-0.77, P for interaction <0.001) relative to no intervention. In conclusion, while these vulnerable patients are at an increased risk for mortality, the meticulous use of revascularization in frail older patients still confers immediate survival benefit [52].

2.7. Aging Kidney

With aging, there is a progressive decrease in glomerular filtration rate (GFR) and renal blood flow, with wide variability among individuals [53]. The widespread adoption of PCI has significantly increased the number of octogenarians exposed to contrast medium (CM) and, thus, the number at

Table 1. Risks of percutaneous coronary intervention secondary to age-related pathophysiology.

Age-Related Pathophysiology	Factors Increasing Risk	Management
Coronary Complexity	Coronary calcification Tortuous lesions Multi-vessel disease Left main stem stenosis Need for more complex interventional strategies (super-high pressure non-compliant balloons, cutting balloons, scoring balloons, atherectomy devices, steerable microcatheters and intravascular lithotripsy)	Inherently higher procedural risk Restrain from being too aggressive
Peripheral Vascular Disease	Access failure	Use preferably the left radial approach
Haematological Factors	Hypercoagulability Increased platelet reactivity Inflammaging Unpredictable pharmacokinetic and pharmacodynamic responses Polypharmacy	Expect increased bleeding risk Antithrombotic drug interactions carefully monitored Dose modification
Drug Metabolism	Reduced enzyme induction capability Less able to tolerate drug overdosing Different distribution volumes Heightened drug effects Reduction in first-pass metabolism and liver cytochrome P450 activity Decline in renal function	Expect increased bleeding risk Antithrombotic drug interactions carefully monitored Dose modification
Multiple Comorbidities	Age-related deterioration on vision, hearing, mobility, renal function, cerebral function and cognition Higher probability of polypharmacy Higher risk of nonadherence to medications Frequent hospital and physician visits Increased health care expenditure	Meticulous formulation of a management plan for an elderly patient
Frailty	Physical functional decline Malnourishment Cognitive impairment Reduced physical capacity to stressors Higher mortality rates	Frailty Index calculation PCI may improve frailty index but under a U-shaped curve
Aging Kidney	Progressive decrease in GFR and RBF Higher risk of CIN Coadministration of various nephrotoxic agents	Preprocedural risk score calculation for prediction of CIN post PCI Review common risk factors for CIN prior to PCI (dehydration, hypotension, anaemia, CCF NYHA class III, IV, DM; LVEF<45%; AMI) and optimize accordingly

Abbreviations: PCI: percutaneous coronary intervention; GFR: glomerular filtration rate; RBF: renal blood flow; CIN: contrast-induced nephropathy; CCF: congestive cardiac failure; DM: diabetes mellitus; LVEF: left ventricular ejection fraction; AMI: acute myocardial infraction.

risk of contrast-induced nephropathy (CIN) [54]. Although in up to 80% of cases, serum creatinine (SCr) levels normalise after approximately 1-3 weeks [55], the confirmation of CIN has a negative role in prognosis [56-59].

Pre-existent stage III chronic kidney disease (CKD), defined as an estimated GFR (eGFR)<60 mL/min/1.73 m^2 for greater than 3 months, is the most identified risk factor for CIN. Indeed, CIN risk becomes clinically significant when baseline SCr concentration is ≥1.3 mg/dL in men and ≥1.0 mg/dL in women [60, 61]. However, in octogenarians, CIN can occur in the absence of underlying CKD if several other risk factors are also present [62], such as diabetes mellitus, congestive heart failure NYHA class III-IV, left ventricular ejection fraction (LVEF)<45%, AMI, haemodynamic instability requiring the use of inotropic agents or intra-arterial balloon pump therapy, reduced plasma volume, female sex, anaemia, and periprocedural bleeding, as well as on the type and volume of contrast administered [63-69].

The generally accepted definition of CIN is a 25% relative increase, or a 0.5 mg/dL absolute increase, in SCr

within 72h of contrast exposure, in the absence of an alternative explanation [70]. Elevations in SCr typically take 2-3 days to reach the current diagnostic threshold following an acute renal insult, thus reducing its usefulness as a marker of acute kidney injury (AKI). However, at 12h, a 5% increase in SCr from baseline was a sensitive (75%) and specific (72%) marker of CIN at 48h and persistent worsening of renal function at 30 days [71].

For all octogenarians referred for PCI procedures, a CIN risk assessment should be performed, which includes baseline measurement of SCr, calculation of eGFR and preprocedural risk score for prediction of CIN post-PCI [41, 72]. If patients are identified as being at risk of CIN, particularly if eGFR<40 mL/min, clinical indications for the procedure should be reviewed and preventative measures instigated. A single invasive approach should ideally be adopted, with CA followed by PCI to reduce the risk of atheroembolic complications while minimising CM volumes to <4 mL/kg or Volume-to-creatinine clearance ratio < 3.7:1 [69]. However, if a second PCI is necessitated, it is advisable to delay until adequate clearance of CM and recovery from any renal injury has occurred, which may be up to 2 weeks or as long as is clinically acceptable [54]. Octogenarians should be advised to stop all non-essential nephrotoxic medications for 24h prior to and for 48h following the PCI procedure pending SCr measurement. The current European guidelines recommend the use of either low-osmolar or iso-osmolar (IO) CM [3], although a preference for IOCM is more reasonable [66]. If angiographic images of coronary lesions are known, one may attempt to perform PCI without contrast administration. Such interventions are mainly guided by intravascular ultrasound imaging (IVUS), which helps to identify the lesion and its length, reference vessel diameters and landing zones for stent implantation [73].

Adequate pre- and post-hydration with isotonic saline remains the mainstay of CIN prevention, at a dose of 1 mL/kg/h 12h before and continued for 24h after the procedure (0.5 mL/kg/h if LVEF ≤ 35% or NYHA >2). In statin naive patients, high-dose statins (Rosuvastatin 40/20 mg or atorvastatin 80 mg), as indicated for secondary prevention irrespective of the risk of CIN, are also beneficial. All other strategies for the prevention of CIN do not have enough evidence to justify a recommendation in favour or against [3, 74-79].

All octogenarians determined as being at risk of CIN should have SCr levels measured between 48 and 72h following CM exposure. If CIN is diagnosed, then it should be managed using recommended AKI guidelines [80]. This includes follow-up SCr measurements, withdrawal of nephrotoxic medications and unnecessary loop diuretics, electrolyte and hydration optimisation, nutritional advice and, if severe, AKI occurs, early hospitalisation with referral to a specialist nephrologist.

Finally, prophylactic hemofiltration (HF) should be reserved for very-high-risk patients, such as for those with pre-dialysis end-stage renal disease or those with severe CKD undergoing complex PCI [81-83].

3. SAFETY AND EFFICACY OF PERCUTANEOUS CORONARY INTERVENTION

Improvements in PCI technology combined with greater operator experience led to reduced post-PCI mortality figures in octogenarians, as demonstrated by Singh *et al*. in the National Cardiovascular Disease Registry (NCDR) Cath PCI Registry [7]. 1410069 patients admitted from 2001-2006 were divided into 4 groups: group 1 (age <40, n=25679), group 2 (40 to 59, n=496204), group 3 (60 to 79, n=732574), and group 4 (≥80, n=155612). The overall post-PCI in-hospital mortality was significantly improved compared to previous [84-88] observational studies at 1.22% of all-comers; in-hospital mortality was 0.60%, 0.59%, 1.26%, and 3.16% in groups 1 to 4, respectively, P<0.0001. The absolute mortality reduction was greatest in group 4 [7].

3.1. ST-Segment Elevation Myocardial Infarction and Primary Percutaneous Coronary Intervention

Primary PCI (PPCI) is currently the treatment of choice for octogenarians presenting with STEMI. Contraindications to thrombolysis appear to increase with age, and the octogenarians are less likely to receive pharmacological reperfusion even if they are eligible [3, 89, 90].

Three RCTs have assessed the efficacy of PPCI in the elderly Table **2**. A small single-centre study that included 87 patients >75 years old showed that PPCI was superior to thrombolysis with streptokinase in reducing the composite endpoint of death, reinfarction or stroke at 30 days [9% *vs* 29%, p=0.01, relative risk (RR): 4.3, 95% CI: 1.2-20.0] and at 1 year (13% *vs* 44%, p=0.001, RR: 5.2, 95% CI: 1.7-18.1) respectively [91-96].

The largest RCT involving treatment options for elderly patients with STEMI was the Senior Primary Angioplasty in Myocardial Infarction (SENIOR-PAMI) study, which enrolled 481 patients, aged ≥70 years presenting with STEMI, with patients randomized to PPCI (n=252) or fibrinolytic therapy (n=229). Although PPCI did not reduce the primary end point of 30-day death or disabling stroke (11.3% for PPCI vs 13% for thrombolytic, p=0.57), likely due to an insufficient sample size, PPCI was superior to thrombolytic therapy at reducing the combined secondary end point of death/disabling stroke/reinfarction (11.6% vs 18.0%, p=0.05), driven by a reduction in reinfarction (1.6% vs 5.4%, p=0.039). In a subgroup analysis of patients stratified by age, the PAMI investigators did find PPCI superior to thrombolytic therapy in patients 70-80 years but not in octogenarians [92, 93].

In the TRIANA (TRatamiento del Infarto Agudo de miocardio eN Ancianos), RCT patients ≥75 years old with STEMI<6 h were randomized to PPCI or fibrinolysis. The primary endpoint was a composite of all-cause mortality, reinfarction, or disabling stroke at 30 days. The trial was prematurely stopped due to slow recruitment after enrolling 266 patients (134 PPCI and 132 fibrinolysis). The primary endpoint was reached in 25 patients in the PPCI group (18.9%) and 34 (25.4%) in the fibrinolysis arm (OR: 0.69; 95% CI: 0.38-1.23; p=0.21). Recurrent ischaemia was less common

in PPCI-treated patients (0.8 vs 9.7%, p<0.001). No differences were found in major bleeds [94].

A pooled analysis with the two previous reperfusion trials performed in older patients showed an advantage of PPCI over fibrinolysis in reducing death, re-infarction, or stroke at 30 days (OR: 0.64; 95% CI: 0.45-0.91) [94].

Thus, PPCI represents the reperfusion strategy of choice in octogenarians with STEMI, with thrombolytic therapy (particularly when given early), a viable alternative when PPCI is not available. Several registries confirmed the superior role of PPCI vs thrombolysis in this group of patients [95, 96] Table **3**.

Caretta *et al*. studied 139 consecutive octogenarians and older STEMI patients treated with PPCI, in search of prognostic factors in this sub-group of patients. 30-day and one-year mortality rates were rather high (20.9% and 28.1%, respectively). After multivariate analysis, age (1-year step, Hazard Ratio [HR]: 1.13; 95% CI: 1.04-1.23; P=0.007), LVEF<40% (HR: 3.70; 95% CI: 1.30-7.87; P=0.0001), Killip class ≥III (HR: 2.29; 95% CI: 1.03-5.4; P=0.04), Systolic Blood Pressure <100 mm Hg (HR: 2.64; 95% CI: 1.22-5.19; P=0.01) and failure of PPCI, defined as post-PCI TIMI flow < 3 (HR: 2.93; 95% CI: 1.44-5.98; p=0.0001) were identified as independent predictors of mortality [97]. In the German Bremen STEMI Registry [98], the rate of successful PPCI (Thrombolysis In Myocardial Infarction flow 2 or 3) was lower in elderly patients than in younger patients (G1: 93.8%, G2: 88.5%, G3: 83.2%, p <0.0001) (Table **3**). Patients >85 years without successful PPCI had a very high in-hospital mortality (40.0% without PCI success *vs* 18.1% with PCI success, p<0.05). In multivariate analyses, successful PCI was an independent predictor of a lower in-hospital mortality rate in all age groups. Even in very old patients, performance of successful PCI was significantly associated with a reduced in-hospital mortality rate (OR: 0.26, 95% CI: 0.08-0.81) and a trend toward lower 1-year mortality [98].

In conclusion, in clinical practice, PPCI in old and very old patients is challenging because an elevated rate of PCI failure, bleeding complications, and mortality must be expected. However, the beneficial effect of successful PCI on mortality in a multivariate analysis proves that revascularization therapy is crucial for the survival of these aged patients.

3.2. Primary Percutaneous Coronary Intervention and Cardiogenic Shock

Damluji *et al*. examined the use of PPCI in older adults with STEMI and cardiogenic shock between 1999 and 2013 and its influence on in-hospital mortality. Of the 317,728 encounters with STEMI and shock in the United States, 111,901 (35%) were adults age ≥75 years. The rate of PCI utilization in older adults increased (1999: 27% *vs* 2013: 56%, p<0.001), with declining in-hospital mortality rates (1999: 64% *vs* 2013: 46%; p<0.001) Table **3** [99].

3.3. Non-Culprit Lesion Treatment

In The Complete *versus* Culprit-Only Revascularization Strategies to Treat Multivessel Disease after Early PCI for STEMI (COMPLETE) trial, a total of 4041 patients (62 ± 10 years of age) from 140 centers in 31 countries underwent randomization. At a median follow-up of 3 years, the first coprimary outcome (composite of cardiovascular death or MI) had occurred in 158 of the 2016 patients (7.8%) in the complete-revascularization group as compared with 213 of the 2025 patients (10.5%) in the culprit-lesion-only PCI group (HR, 0.74; 95% CI, 0.60 to 0.91; p = 0.004). The second coprimary outcome (composite of cardiovascular death, MI, or ischemia-driven revascularization) had occurred in 179 patients (8.9%) in the complete-revascularization group as compared with 339 patients (16.7%) in the culprit-lesion-only PCI group (HR, 0.51; 95% CI, 0.43 to 0.61; p<0.001). For both coprimary outcomes, the benefit of complete revascularization was consistently observed regardless of the intended timing of nonculprit-lesion PCI (p = 0.62 and p = 0.27 for interaction for the first and second coprimary outcomes, respectively) [100, 101]. This conclusion, however, needs to be verified in elderly STEMI patients who could lose the benefit of complete revascularization because of a potentially higher risk of complications and increased use of contrast agents.

Indeed, three studies have been published on the role of incomplete revascularization in elderly patients with ACS and the exploration of the residual Syntax Score (rSS) as a prognostic factor has led to conflicting results [102-104]. In elderly ACS patients with MVD undergoing PCI, incomplete revascularization was associated with worse outcomes at 1-year follow-up. However, there was no clear incremental value of the rSS in the prediction of 1-year adverse outcomes compared to a model, including clinical variables and the baseline SS [105]. According to the above-reported findings, in elderly ACS patients, the pursuit of more extensive revascularization should always be balanced with the risk of vascular complications and the impact of comorbidity and frailty.

3.4. Non-ST-Segment Elevation Myocardial Infarction

Octogenarians are under-represented in the NSTEMI trial data, and very few data come from RCTs (Table **2**) [106-109]. Furthermore, we have to keep in mind that RCT included a highly selected population (10.9% of screened patients in After Eighty trial and 48.5% of patients assessed for eligibility after signed consent in the Italian-ACS trial), which limits the generalization of the results in the whole spectrum of elderly patients. Garg *et al*. [6] performed a systematic review and metanalysis to evaluate outcomes of Routine Invasive Strategy (RIS) compared with Selective Invasive Strategy (SIS) in 1887 patients >75 years with NSTEACS between January 1, 1990, and October 1, 2016. Compared with a SIS, RIS was associated with significantly decreased risk of the composite endpoint of death or MI (OR: 0.65; 95% CI: 0.51-0.83) (primarily driven by reduced risk of MI) (OR: 0.51; 95% CI: 0.40-0.66) and need for revascularization (OR: 0.31; 95% CI: 0.11-0.91) [6].

To summarize, current evidence supports the use of an RIS in the elderly in order to reduce the occurrence of MI and the need for revascularization at follow-up, and there is no established benefit in terms of mortality. It is to note that

Table 2. Randomized trials of percutaneous coronary intervention in the elderly in different clinical syndromes.

Study Name & Year of Publication	Condition	Sample Size (number of patients)	Age (Years)	Randomization	Endpoints	Results	Interpretation	Limitations
De Boer *et al*. Zwolle study 2002	STEMI	87	>75	PPCI (n=46) *vs* thrombolysis (n=41)	Composite endpoint of death, reinfarction or stroke at 30 days and 1 year	30 days: 9% *vs* 29% (p=0.01, RR: 4.3, 95% CI: 1.2-20) 1 year: 13% *vs* 44% (p=0.001, RR: 5.2, CI: 1.7-18.1)	PPCI better than thrombolysis	Single center, not blinded, small
Senior Primary Angioplasty in Myocardial Infarction (SENIOR-PAMI) study 2005	STEMI	481	≥70	PPCI (n=252) *vs* thrombolysis (n=229)	Primary: Death or disabling stroke at 30 days Secondary: combined endpoint of death, disabling stroke or reinfarction at 30 days	Primary: 11.3% *vs* 13% (p=0.57) Secondary: 11.6% *vs* 18% (p=0.05)	PPCI not better for death or disabling stroke, but reduced reinfarction (1.6% *vs* 5.4%, p=0.039) . PPCI benefit in patients 70-80 years, but not in octogenarians	Discontinued early due to slow recruitment
TRatamiento del Infarto Agudo de miocardio eN Ancianos (TRIANA) trial 2011	STEMI	266	≥75	PPCI (n=134) *vs* thrombolysis (n=132)	Primary: Composite of all--cause mortality, reinfarction or disabling stroke at 30 days Secondary: recurrent ischemia	Primary: 18.9% *vs* 25.4% (p=0.21, OR: 0.69, 95% CI: 0.38-1.23) Secondary: 0.8% *vs* 9.7% (p<0.001)	PPCI not better than fibrinolysis for the primary endpoint but reduced recurrent ischemia	Discontinued early due to slow recruitment
Bach *et al*. Treat angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy - Thrombolysis In Myocardial Infarction (TACTICS-TIMI) 38 trial 2004	NSTEMI and UA	962	≥65	Early invasive (medical therapy + coronary angiography 4-48 h) (n=491) *vs* conservative management (medical therapy + predischarge exercise testing) (n=471)	Rates of 30-day and 6-month mortality, nonfatal MI, rehospitalization, stroke, and hemorrhagic complications	≥65 years: death or MI at 6 months: 8.8% *vs* 13.6% (p=0.018, RR-R:39%) >75 years: death or MI at 6 months: 10.8% *vs* 21.6% (p=0.016, RRR: 56%), major bleeding: (16.6% *vs*. 6.5%; P = 0.009)	Routine early invasive Strategy improves ischemic outcomes in the elderly, but with increased risk for major bleeding in >75 years	Study population was a subgroup from the TACTICS-TIMI 38 trial, its generalizability to elderly patients with excluded comorbid conditions is unknown; the medical treatment outdated according to current practice
Italian Elderly ACS trial 2012	NSTEMI and UA	313	≥75 mean 82 years	Early aggressive strategy EA (coronary angiography and, when indicated, revascularization within 72 h) (n=154) or an initially conservative IC strategy (angiography and revascularization only for recurrent ischemia) (n=159)	Primary: Composite of death, MI, disabling stroke, and repeat hospital stay for cardiovascular causes or severe bleeding within 1 year	The primary outcome occurred in 43 patients (27.9%) in the EA group and 55 (34.6%) in the IC group (HR: 0.80; 95% CI: 0.53 to 1.19; p=0.26). The primary endpoint was significantly reduced in patients with elevated troponin on admission (HR: 0.43; 95% CI: 0.23 to 0.80), but not in those with normal troponin	Significant interaction for the treatment effect according to troponin status at baseline Within 1 year, a 20% difference in the rates of our primary endpoint between the EIS and the IC cohorts was observed. This difference was not statistically significant in the present trial, which was powered for a 40% difference in the primary endpoint rate.	Underpowered for the primary endpoint

(Table 2) contd....

Study Name & Year of Publication	Condition	Sample Size (number of patients)	Age (Years)	Randomization	Endpoints	Results	Interpretation	Limitations
-	-	-	-	-	-	(HR: 1.67; 95% CI: 0.75 to 3.70; p for interaction =0.03).	However, patients with elevated troponin levels on admission randomized to an EIS approach had a significant 57% reduction of the primary endpoint rate	-
FIR (FRISC II-ICTUS-RITA 3) trials 2012	NSTEMI and UA	839	≥75 subgroup mean age of just 76 years	Routine invasive (n=437) *versus* a selective invasive strategy (n=402)	5-year cardiovascular death or myocardial infarction (MI) following routine invasive *versus* selective invasive management	HR 0.71, 95% CI 0.55 to 0.91 p=0.001 for interaction between treatment strategy and age	29% reduction in cardiovascular death or MI at 5 years was achieved by a routine invasive approach	These trials were not specifically designed for elderly patients.
After Eighty study 2016	NSTEMI or UA During a median follow-up of 1.53 years of participants recruited between Dec 10, 2010, and Feb 21, 2014	457	≥80	Early invasive (n=229) *vs* conservative (n=228) strategy	Primary: Composite of MI, urgent revascularization, stroke, and death	40.6% *vs* 61.4% (p=0.0001) HRs for the four components of the primary composite endpoint were 0.52 (0.35-0.76; p=0.0010) for MI, 0.19 (0.07-0.52; p=0.0010) for the need for urgent revascularisation, 0.60 (0.25-1.46; p=0.2650) for stroke, and 0.89 (0.62-1.28; p=0.5340) for death from any cause. MI: HR=0.52 (p=0.001) Urgent revascularization: HR=0.19 (p=0.001)	Early invasive superior to the conservative strategy in the reduction of composite events with no differences in bleeding complications (but efficacy was less with increasing age - no conclusions for >90 years)	Open label, few patients >90 years Only 457 patients were included out of 4187 screened: 53% met exclusion criteria (mainly short life expectancy), and only 23% of candidates for inclusion were randomized. Therefore, selection bias may be an issue in this trial and the included population may not reflect the whole spectrum of elderly patients.
TIME 2001	Chronic angina	305	≥75	Invasive (n=155) *vs* medical (n=150) therapy	Quality of life (assessed by questionnaire) The composite outcome of death, documented non-fatal MI, hospital admission for increasing or UA (acute coronary syndrome) with or without the need for revascularization at 6 months	Angina severity decreased and measures of quality of life increased in both treatment groups, but were significantly greater after revascularization. Composite outcome: 19% *vs* 49% (p<0.0001) Hospital admissions: 7.8% *vs* 49.3% (p<0.01) Death: NS Non-fatal MI: NS	Invasive therapy better in symptom relief and quality of life	7% of patients with chronic angina despite normal coronary arteries

Abbreviations: PPCI: primary percutaneous coronary intervention, AMI: acute myocardial infarction, BMS: bare metal stent, CI: confidence interval, DAPT: dual antiplatelet treatment, DES: drug eluting stent, IV: intravenously, HR: hazard ratio, MACCE: major adverse cardiac and cerebrovascular events, NS: not statistically significant, NSTEMI: non-ST segment elevation myocardial infarction, OR: odds ratio, pPCI: primary percutaneous coronary intervention, RR: relative risk, RRR: relative risk reduction, STEMI: ST segment elevation myocardial infarction, TLR: target lesion revascularization TVR: target vessel revascularization, UA: unstable angina, UFH: unfractionated heparin, ACS: acute coronary syndrome, FIR: FRISC II-ICTUS-RITA-3.

the RIS did not increase the risk of major bleedings, probably because antithrombotic drugs were equally used in both strategies and also the reduction in access-site complications driven by the expansion of the radial approach.

Most data come from registries [110-112], and despite their methodological confounders, may reflect evidence closer to the daily clinical practice. Liistro *et al*. evaluated an early invasive strategy (including routine use of diagnostic catheterisation within 24-48 hours of admission and revascularisation as indicated, with CABG or PCI) in patients ≥75 with NSTEMI from June 2002 to February 2004. Coronary revascularisation was conducted in 133 (83%) elderly patients and 239 (85%) younger patients. At a mean (SD) follow up time of 10.7 (5.2) months overall mortality, cardiac death, and death plus MI were significantly higher among elderly patients than among younger patients (9.4% *vs* 2.1%, p<0.001; 6.8% *vs* 1.8%, p < 0.01; 11.3% *vs* 5%, p=0.02, respectively). The significant difference in cardiac death between the two groups was related more to elderly patients being treated by CABG (19.3% *vs* 4.9%, p=0.05) than by PCI (2.9% *vs* 1.1%, p= 0.3) [110]. In a study by De Servi *et al*., an aggressive treatment strategy (involving CA within 4 days, followed by revascularisation where possible) was followed in 39% >75 years and 56% in the < 75years group (p=<0.001). 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 the 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 [111]. In addition, an analysis of 18,466 patients in the GRACE registry, of whom 16% were octogenarians, 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) [112].

Table 3. Observational studies in elderly st-segment elevation myocardial infarction patients.

Study Name & Year of Publication	Sample Size (Number of Patients)	Age (years)	Population Groups	Endpoints	Results	Interpretation	Limitations
Chinese Acute Myocardial Infarction (CAMI) 2016	3082	≥75	PPCI (n=1000) *vs* thrombolysis (n=160) *vs* no reperfusion (n=1922)	Primary: Death Secondary: recurrent MI, ischemia-driven revascularization (IDR), cerebral events (ischemic or hemorrhagic stroke), major bleeding (excluding hemorrhagic stroke), MI related complications, which included heart failure, mechanical complications, ventricular tachycardia/ventricular fibrillation, and cardiac arrest	Primary: 7.7% *vs* 15% *vs* 19.9%, respectively, p<0.001 Cardiac death (7.3% *vs* 14.4% *vs* 18.6%, P<0.001) and non-cardiac death (0.6% *vs* 0.6% *vs* 1.4%, P=0.028) Secondary: Recurrent MI (0.7% *vs* 1.9% *vs* 0.8%, p=0.412) IDR (0.9% *vs* 0 *vs* 0.2%, p=0.007) Heart failure (17.7% *vs* 28.8% *vs* 33.1%, p<0.001) Mechanical complications (0.5% *vs* 1.9% *vs* 1.8%, p=0.006) Cardiac arrest (3.6% *vs* 6.3% *vs* 10%, p<0.001) The rates of hemorrhagic stroke (0.3%, 0.6%, and 0.1%) and other major bleeding (3.0%, 5.0%, and 3.1%) were similar in the PPCI, fibrinolysis, and no reperfusion group (P>0.05).	Early reperfusion, especially primary PCI is safe and effective for elderly patients with absolute reduction of mortality compared with no reperfusion.	Baseline disparities and selection bias was inevitable A great proportion of late reperfusion may confound the results, 6.9% of the patients having fibrinolysis were between 12 to 24h, and around 11.3% having fibrinolysis more than 1day

(Table 3) contd....

Study Name & Year of Publication	Sample Size (Number of Patients)	Age (years)	Population Groups	Endpoints	Results	Interpretation	Limitations
Western Denmark Heart Registry 2013	1322	≥ 80	1,213 octogenarians and 109 nonagenarians treated with PPCI	Primary: 30-day, 1-year, 5-year mortality	30-day mortality: 17.2% *vs* 25.8% (log-rank P = 0.028), 1-year mortality: 27.6% *vs* 32.5% (log-rank P = 0.18) and 5-year mortality: 53.6% *versus* 57.3% (log-rank P = 0.087), respectively.	The annual proportion of octogenarians with STEMI treated with PPCI doubled from 2002 to 2009, while the proportion of nonagenarians remained unchanged Nonagenarians had the highest short- and long-term mortality Acceptable outcome with a 5-year survival of more than 40% in both groups	-
German Bremen STEMI Registry 2015	5356	G1: <75 (n=4,108), G2: 75-85 (n=1,032) G3: >85 (n=216)		Bleedings grade > 2° - Thrombolysis In Myocardial Infarction Bleeding Criteria Bleedings grade > 2° - Bleeding Academia Research Consortium Criteria Bleedings grade > 2° - any above definition in-hospital MACCE 1-year MACCE	177 (4.8%), 82 (9.7%), 33 (18.3%) (G1 *vs* G2 *vs* G3 p<0.0001; G2 *vs* G3 p=0.002) 181 (5.0%), 87 (10.3%), 32 (17.8%) (G1 *vs* G2 *vs* G3 p<0.0001; G2 *vs* G3 p=0.007) 198 (5.4%), 93 (11.0%), 35 (19.6%) (G1 *vs* G2 *vs* G3 p<0.0001; G2 *vs* G3 p=0.003) 189 (5.2%), 122 (14.4%), 35 (19.6%)	Elevated rate of PCI failure, bleeding complications, and mortality in elderly patients treated by primary PCI for STEMI. However, a beneficial effect of successful PCI on mortality was observed in all age groups, even in very old patients, indicating the crucial role of revascularization therapy.	-
-	-	-		-	(G1 *vs* G2 *vs* G3 p<0.0001) Mortality: 149 (4.1%), 112 (13.2%), 35 (19.6%) (G1 *vs* G2 *vs* G3 p<0.0001; G2 *vs* G3 p=0.034) 384 (10.5%), 228 (26.9%), 77 (43.0%) (G1 *vs* G2 *vs* G3 p<0.0001, p<0.0001) Mortality: 253 (6.9%), 192 (22.7%), 69 (38.5%) (G1 *vs* G2 *vs* G3 p<0.0001; G2 *vs* G3 p<0.0001) Stroke: 22 (0.6%), 12 (1.4%), 4 (2.2%) p=0.002	-	-
Damluji *et al.* 2019	111.901	≥75	Cardiogenic shock patients	In-hospital mortality	Rate of PCI utilization in older adults increased (1999: 27% *vs* 2013: 56%, p<0.001), with declining in-hospital mortality rates (1999: 64% *vs* 2013: 46%; p<0.001).	Utilization of PPCI in older adults with STEMI and cardiogenic shock is increasing and paralleled by a substantial reduction in mortality	-

There are on-going randomised prospective multicentre trials attempting to address the lack of robust research data. The Revascularisation or Medical Therapy in Elderly Patients with acute angina syndromes (the RINCAL study, NCT 02086019) aims to address whether for octogenarian NSTEMI patients, an invasive-guided strategy will prove superior to a conservative approach with respect to a combined endpoint of all-cause mortality and non-fatal MI at 1 year. The estimated study completion date was March 2020.

The SENIOR-RITA trial (NCT 03052036) is a multicentre prospective open-label trial randomizing patients aged ≥75 years presenting with type 1 NSTEMI between invasive (PCI or CABG) and conservative treatment strategies, to compare time to cardiovascular death or non-fatal MI within one year from randomization. It is a superiority trial of the RIS on one-year cardiovascular death and non-fatal MI compared with the conservative approach. The trial hopes to recruit 2300 patients from approximately 30 centres across the UK. Estimated study completion date is in September 2029.

Finally, the Routinely Deferred *Versus* Early Intervention in Elderly Patients With Non-ST-elevation Myocardial Infarction (DEAR-OLD) study (NCT 02900001) aims to evaluate the efficacy and safety of a routinely deferred invasive strategy in comparison with an early invasive strategy in Chinese elderly patients of 75 years or older with NSTEMI, aiming to test the hypothesis that routinely deferred invasive strategy is not inferior to early invasive strategy in such an elderly group of patients. This study aims to enrol 696 elderly patients with NSTEMI from 20 hospitals throughout mainland China. The estimated study completion date was October 2019.

In the absence of robust randomized clinical data on PCI treatment strategies for the elderly population, observational study results remain valuable in providing insights into the outcomes after PCI. Thus, from the observational studies, it can be inferred that for the elderly, late elderly and octogenarians with NSTEMI, early revascularization combined with OMT is the preferred strategy.

3.5. Chronic Coronary Syndromes and Elective Percutaneous Coronary Intervention

Although the Trial of Invasive *versus* Medical Therapy in Elderly patients with chronic symptomatic coronary-artery disease (TIME) is dated, it stands out as the only RCT comparing medical therapy to invasive management in older patients with stable angina of at least Canadian Cardiac Society class II despite at least two antianginal drugs [113]. Despite the above study and the fact that the procedure itself is deemed to be relatively safe for stable patients [114], even for those >90 years [115], some studies suggested that the prognostic benefit of PCI in stable disease may be limited [116]. Additionally, quality of life (QoL) should be taken into consideration regarding revascularization in the elderly. Recent data demonstrate that patients >75 years old experience sustained long-term improvement in QoL after PCI. In fact, this improvement is comparable with younger patients [117].

4. SPECIFIC ISSUES IN THE ELDERLY POPULATION

4.1. Type of Stent

In patients undergoing PCI with stent implantation, procedural aspirin and P2Y12 receptor inhibitor administration is mandatory and constitutes the so-called dual antiplatelet therapy (DAPT) [3]. Afterwards, DAPT is recommended for a duration of 6 months in patients with stable CAD and for 12 months in patients with an ACS [118, 119]. Despite a wealth of data demonstrating the superiority of drug eluting stents (DES) *versus* bare metal stents (BMS) in all types of lesions/patients [120], unjustified [121, 122] concerns regarding bleeding adverse events have led to utilization of DES in elderly patients undergoing PCI [123]. The Prospective Randomized Comparison of the BioFreedom Biolimus A9 Drug-Coated Stent *versus* the Gazelle Bare-Metal Stent in Patients at High Bleeding Risk (LEADERS FREE) trial was designed to evaluate the efficacy and safety of the polymer-free umirolimus-coated stent as compared with a BMS in 2432 patients with increased bleeding risk aged ≥75 years undergoing PCI, with a 1-month regimen of DAPT in both groups. The primary safety endpoint, tested for both noninferiority and superiority, was a composite of cardiac death, MI, or stent thrombosis. The primary efficacy endpoint was clinically driven target-lesion revascularization (TLR). At 390 days, the primary safety endpoint had occurred in 112 patients (9.4%) in the drug-coated-stent group and in 154 patients (12.9%) in the BMS group (risk difference, −3.6 percentage points; 95% CI, −6.1 to −1.0; HR, 0.71; 95% CI, 0.56 to 0.91; P<0.001 for noninferiority and P=0.005 for superiority). During the same time period, clinically driven TLR was needed in 59 patients (5.1%) in the drug-coated-stent group and in 113 patients (9.8%) in the BMS group (risk difference, −4.8 percentage points; 95% CI, −6.9 to −2.6; HR, 0.50; 95% CI, 0.37 to 0.69; P<0.001) [124]. In addition to that, in the Xience or Vision Stents for the Management of Angina in the Elderly XIMA Trial, 800 patients (83.5 ± 3.2 years of age) were randomized to BMS or DES. For patients receiving BMS, 1 month of DAPT was mandatory. For patients receiving DES, DAPT was prescribed for 1 year. The primary endpoint (1-year composite of death, MI, cerebrovascular accident, TVR, or major haemorrhage) occurred in 18.7% of patients in the BMS group *vs*. 14.3% of patients in the DES group (P = 0.09). There was no difference in death, major haemorrhage, or cerebrovascular accident but MI (8.7 *vs*. 4.3%; P = 0.01) and TVR (7.0 *vs*. 2.0%; P = 0.001) occurred more often in patients treated with the BMS [125]. Furthermore, the SENIOR trial demonstrated lower rates of the 1-year all-cause mortality, MI, stroke, and revascularization in elderly patients ≥75 years who underwent PCI and received bioabsorbable polymer DES (Synergy; Boston Scientific, Marlborough, MA, USA) (n=596) and a short-term (1 month for patients with stable presentation and 6 months for those with unstable presentation) DAPT compared to those who received a similar thin-strut BMS (Omega or Rebel; Boston Scientific) (n=604). The primary endpoint occurred in 68 (12%) patients in the DES group

and 98 (16%) in the BMS group (RR 0·71 [95% CI 0·52-0·94]; p=0·02). Bleeding complications (26 [5%] in the DES group *vs* 29 [5%] in the BMS group; RR 0·90 [0·51-1·54]; p=0·68) and ST (three [1%] *vs* eight [1%]; RR 0·38 [0·00-1·48]; p=0·13) at 1 year were infrequent in both groups [126]. Most recently, among patients at high bleeding risk who received 1 month DAPT after PCI, the use of polymer-based zotarolimus-eluting stents (ZES) (Resolute Onyx stent) was noninferior to the polymer-free drug-coated stents (BioFreedom stent) with regard to safety and effectiveness composite outcomes. A total of 1996 patients at high bleeding risk aged ≥75 years were randomly assigned in a 1:1 ratio to receive ZES (1003 patients) or polymer-free drug-coated stents (993 patients). At 1 year, the primary outcome was observed in 169 of 988 patients (17.1%) in the ZES group and in 164 of 969 (16.9%) in the polymer-free drug-coated stent group (risk difference, 0.2 percentage points; upper boundary of the one-sided 97.5% CI, 3.5; noninferiority margin, 4.1; P=0.01 for noninferiority). The principal secondary outcome was observed in 174 patients (17.6%) in the ZES group and in 169 (17.4%) in the polymer-free drug-coated stent group (risk difference, 0.2 percentage points; upper boundary of the one-sided 97.5% CI, 3.5; noninferiority margin, 4.4; P=0.007 for noninferiority) [127]. In conclusion, in the current era of PCI with the use of contemporary DES, refined PCI techniques and adjunctive pharmacotherapy a strategy of a combination of a DES to reduce the risk of subsequent repeat revascularisations with a short BMS-like DAPT regimen to reduce the risk of a bleeding is an effective and safe option for elderly patients who undergo PCI [128].

4.2. Mode of Myocardial Revascularization

Patients are more often referred for PCI than CABG, but age should not be the sole criterion determining the choice of the type of revascularization, since CABG seems to hold long-term advantages in elderly patients with multivessel CAD [129, 130]. At 10 years follow-up of the SYNTAX trial, CABG provided a significant survival benefit in patients with three-vessel disease, but not in patients with LMS CAD. Although there was no upper age limit for inclusion in the SYNTAX trial, the mean age of patients was only 65 ± 10 years [131]. Whether this is true in older patients is uncertain. Yamaji *et al*. tried to fill this gap in knowledge through their study, which evaluated the effects of the age and sex on clinical outcomes after PCI relative to CABG in a pooled population of Cohorts 1 and 2 (era of BMS and DES, respectively) of the CREDO-Kyoto (Coronary Revascularization Demonstrating Outcome Study in Kyoto) all--comer registry [132]. Of 25816 patients enrolled in CREDO-Kyoto; Cohort-1, n=9877; Cohort-2, n=15939, the present study population consisted of 5651 patients with triple-vessel CAD who were considered to be pertinent in comparisons of PCI with CABG (PCI, n=3165; CABG, n=2486). Patients were divided into 3 groups according to the tertiles of age: ≤65 years (n=1972), 66 to 73 years (n=1820), and ≥74 years (n=1859). The excess adjusted mortality risk of PCI relative to CABG was significant in patients ≥74 years of age (HR, 1.40; 95% CI, 1.10-1.79; P=0.006), whereas the risks were neutral in patients ≤65 years of age (HR, 1.05; 95% CI, 0.73-1.53; P=0.78) and in patients 66 to 73 years of age (HR, 1.03; 95% CI, 0.78-1.36; P=0.85; interaction P=0.003) [132].

In a 10-study metanalysis of 2,386 older patients (mean age 75 years) with unprotected LMS disease, no significant differences were observed between CABG and PCI (mostly with DES) in all-cause mortality, nonfatal MI, or MACE at 22 months [133]. In the CUSTOMIZE (Appraise a Customized Strategy for Left Main Revascularization) registry, PCI and CABG had similar 1-year outcomes in 202 patients ≥75 years of age with LMS disease, whereas MACE and repeat revascularization rates were higher with PCI in 692 younger patients [134]. No randomized trials of PCI *versus* CABG restricted to older patients have been performed. However, insights may be gleaned from subgroup analyses from recent large, randomized trials. The relative effects of PCI and CABG, in general, appear to be comparable in older and younger patients [135-139].

CONCLUSION

The increasing prevalence of revascularization in the octogenarians has sharpened the focus on methods of optimisation of PCI strategies in this population. Despite the high--risk intrinsic nature of this population, percutaneous revascularization is likely to afford improvements in clinical outcomes and functional status. Age does make a difference to PCI outcomes in older people, but it is never the sole arbiter of any clinical decision, whether in relation to the heart or any other aspect of health. Not all octogenarians should go to the catheterization laboratory, but final management of any clinical coronary syndrome will depend on issues of frailty, appropriateness, feasibility of safe revascularisation, cognition, drug interactions and compliance. There is a clear need for clinical trials to be conducted that are specifically dedicated to the late elderly and octogenarian patients, with less rigid exclusion criteria, to better translate their results to current real-world practice.

AUTHOR'S PERSPECTIVES

The decision when to perform revascularization in elderly patients and especially in octogenarians 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. In STEMI, there is no upper age limit regarding urgent reperfusion and PPCI must be the standard of care. In NSTEACS, a strict conservative strategy must be avoided; whereas the use of a routine invasive strategy may reduce the occurrence of MI and the need for revascularization at follow-up, with no established benefit in terms of mortality. In stable CAD patients, invasive therapy on top of the OMT seems better in symptom relief and QoL. The revascularization of functionally significant lesions resulting in a sustained clinical benefit.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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