

Contemporary Revascularization Dilemmas in Older Adults

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The United States has seen an annual increase of >160 000 octogenarians, and this demographic is predicted to increase by nearly 5-fold by the year 2040.¹ Age is a well-established risk factor for coronary artery disease (CAD) and is the most common cause of death in elderly people.² Management decisions in older patients can be challenging to the clinicians, as increasing age is a strong predictor of adverse events.^{3,4} Older age has been found to be predictive of lower use of cardiac catheterization, with significant variation internationally.⁵ This is despite the data showing that although in-hospital mortality after percutaneous coronary intervention (PCI) has fallen for all age groups over the past several years, the largest absolute reduction was noted in patients aged ≥ 80 years.⁶ As the proportion of patients aged >80 years increases, cardiologists will treat an increasing number of octogenarians in their practice. In fact, it has been shown that in a tertiary center, despite an increase in the proportion of octogenarians undergoing PCI over a decade, along with the complexity of lesions treated, there was a decline in major adverse cardiovascular and cerebrovascular event rates from 1% to 0.4%.⁷ Other studies have also shown that despite age being an important risk factor, the older patients presenting with acute coronary syndrome (ACS) may experience a similar or greater benefit from early invasive procedures.⁸

There is a need to increase the inclusion rates of older adults in clinical trials because the oldest old also unfortunately experience the greatest health burden in the Western world, having higher rates of cardiovascular disease. Healthcare costs for older adults account for 36% of the total US

personal healthcare dollars, and older adults consume 42% of all prescription drugs.⁹ The Social Security Administration and Medicare continue to define old age as being >65 years; however, using a chronological age is largely uninformative for constructing clinical guidance. Using the concept of a physiological age could potentially lead to more meaningful results. The Food and Drug Administration has made recommendations for clinical researchers proactively to include older adults aged ≥ 75 years, who experience higher disease burden than younger older adults⁹ as this patient population is vastly underrepresented in many studies.

In this state-of-the-art review, authors summarize data from large multicenter clinical trials that have incorporated older patients undergoing PCI and discuss the importance of taking age into account as an important outcome predictor in older patients, while they can also have the highest absolute risk reduction from PCI compared with other age groups. Certainly, one needs to consider other factors, such as frailty, cognitive impairment, risk of bleeding, and other concomitant medical conditions, that all can affect the decisions for revascularization in this age group (Figure). Our review of the current literature demonstrates that age by itself should not preclude elderly patients from revascularization.

Impact of Frailty in Elderly Patients With ACS

Age plays a major role in the morbidity and mortality of patients with ACS and is an important factor in contemporary risk assessment scores, such as the Thrombolysis in Myocardial Infarction (TIMI) risk score and the GRACE (Global Registry of Acute Coronary Events) score. Frailty, representing decreased physiological reserve leading to increased vulnerability, increases the risk of ACS and its consequences in the elderly population. Frailty has been shown to be associated with an increased risk of mortality, longer hospital stay, increased use of resources, and higher risk of delirium. Frail elderly women are a particularly high-risk group, as female sex has been shown to be an independent predictor of frailty in elderly patients with ACS and has been shown to be associated with higher mortality. In a study investigating the relationship between age of frailty and clinical outcomes in patients undergoing PCI in 2080 young-old patients (aged 60–75 years) and 1104 frail old patients (aged >75 years)

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| Specific Consideration Regarding Obstructive CAD in Older Adults | |
|---|--|
| Importance | Older adults many times do not receive evidence-based, especially life-saving interventions for obstructive CAD, due to the lack of knowledge, confidence, and data |
| ACS Presentation | Older adults commonly have atypical symptoms such as atypical chest pain, nausea, vomiting, generalized weakness as presenting symptoms of ACS leading to delay in timely diagnosis |
| ACS Management | Despite increased prevalence of high risk features such as heart failure, diabetes, and higher GRACE scores in the elderly, invasive procedures are not offered to many older adults while evidence show that many of them can benefit from such procedures even when presenting with cardiogenic shock. |
| Stent type | Studies suggest, among elderly, DESs should be the preferred over BMSs even if short duration of DAPT is desired for specific reasons, i.e. bleeding risks. |
| Concomitant Anticoagulation | Due to increased prevalence of AF in older age, need for long-term anticoagulation is common at this age group. However, limited data is available for the best strategy of concomitant DAPT and anticoagulation. While no guideline or FDA recommendation exist, most clinicians use short duration of triple therapy, such as 2-4 weeks, and then stop aspirin and continue with a P2Y12 inhibitor, mostly clopidogrel, and a direct oral anticoagulant. |
| Concomitant severe AS | The timing of PCI in relation to TAVR remains largely unclear. In one study, FFR-guided PCI prior to TAVR showed better outcome than medical therapy alone or angiographic-guided PCI. |
| Future Directions | Reporting safety results (to determine benefits and risk), conduction of trials exclusively including elderly patients only, and a better understanding of the frailty and cognitive impairment that affects this high-risk population will improve the enrollment rates of elderly in clinical trials and hence the care for older adults with obstructive CAD. |

Figure. Specific consideration on obstructive coronary artery disease (CAD) in older adults. ACS indicates acute coronary syndrome; AF, atrial fibrillation; AS, aortic stenosis; BMS, bare metal stent; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; FDA, Food and Drug Administration; FFR, fractional flow reserve; GRACE, Global Registry of Acute Coronary Events; PCI, percutaneous coronary intervention; TAVR, transcatheter aortic valve replacement.

presenting with non-ST-segment-elevation ACS, older patients with frailty were more likely to be women and to have extensive comorbidities, including a history of heart failure, than other patients. They were also less likely to be given guideline-directed therapy, such as aspirin, statin, and clopidogrel, and were less likely to be offered PCI compared with the younger group (18.8% versus 37.1%). Patients in this group were also 3 times more likely to die compared with young-old patients at 30 days (8.2% versus 3.6%; $P<0.001$). An early invasive strategy with PCI was found to be associated with lower mortality in both the young-old (odds ratio [OR], 0.55; 95% CI, 0.31–0.98) and in the frail old patients (OR, 0.44; 95% CI, 0.19–0.99). Thus, although frail old patients had a higher 30-day mortality than young-old patients, invasive management was found to significantly reduce 30-day mortality.¹⁰ In another study of patients aged >75 years being evaluated during admission for acute myocardial infarction (MI), the median age was found to be 82 years, 53% were women, and 75% were white, with prevalence of frailty being 19%. The frail patients were more likely to be older and more likely to be women and ethnic minority members, with more extensive comorbidities. Frail patients were much less likely to undergo PCI compared with nonfrail

patients (15% versus 33%; $P<0.001$). Although the use of PCI was much less likely in frail older patients, they were still likely to derive a survival benefit from PCI (OR, 0.59; $P<0.001$). The results of these studies demonstrate that in the United States, frailty is common in patients hospitalized with acute MI, conferring a higher mortality risk that increases with age. PCI in this more frail, older group still confers a strong survival benefit.¹¹ In a study that evaluated the timing of invasive treatment, duration of hospitalization, and rate of in-hospital complications in patients aged >75 years with non-ST-segment-elevation MI (NSTEMI), the rate of procedural complications between the 2 groups was 3.3% in frail versus 5.7% in nonfrail patients ($P=0.377$) and 8.2% versus 3.3% ($P=0.136$) for in-hospital complications. Thus, the rate of procedural and in-hospital complications has not been shown to be significantly different between frail and nonfrail older patients, indicating that frail patients can safely undergo PCI with similar complication rates to nonfrail patients.¹²

Although studies have demonstrated that frail older patients stand to confer a mortality benefit from revascularization for ACS with complication rates similar to nonfrail patients, there is also evidence for improved quality of life. In a study that was aiming to investigate the relationship

between frailty and quality of life in elderly patients aged >65 years, frailty was found to be present in 82.4% of patients and was found to be an independent predictor of worse quality of life ($\beta \pm SE$, -0.277 ± 0.122 ; $P=0.026$).¹³ In another study of 130 patients aged >75 years with ACS, frailty was present in 66% of patients, who had a higher rate of mortality at 6 months compared with nonfrail patients (24.6% versus 16.2%; $P=0.03$). Patients with GRACE scores >140 had more prominent cognitive dysfunction and decreased functional mobility, whereas those with TIMI scores >5 points had higher scores on a frailty scale with more physical disability of daily living.¹⁴ Given the profound clinical implications of frailty, there is a need for a comprehensive geriatric assessment that should be incorporated into classic risk scores, such as GRACE and Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines.¹⁴

Timing of assessment is a crucial aspect to managing patients with cardiac diseases; for example, there is increasing evidence that some elderly patients fail to derive mortality benefit after transcatheter aortic valve replacement (TAVR) or surgical aortic valve replacement because of poor functional status and extensive comorbidities.¹⁵ In a recent study that compared several tools in a large cohort of older 1020 patients undergoing TAVR or surgical aortic valve replacement, the Essential Frailty Toolset was found to be the best scale for risk stratification as it was strongest predictor of 1-year death (adjusted OR, 3.72; 95% CI, 2.54–5.45) and of 1-year worsening disability (adjusted OR, 2.13; 95% CI, 1.57–2.87).¹⁶ The Essential Frailty Toolset is a 4-item scale that assesses lower-extremity weakness (the time needed to perform 5 chair rises), cognitive impairment (defined as <24 points on the Mini-Mental State Examination), anemia (<13 g/dL in men and <12 g/dL in women), and hypoalbuminemia (<3.5 g/dL). In another study, the Clinical Frailty Scale (CFS), which has traditionally been used to predict adverse outcomes in elderly patients, was used to assess the impact of CFS on clinical outcomes after PCI. The patients were categorized into 2 groups based on their CFS stage, including CFS 1 to 3 and CFS ≥ 4 and these stages were correlated with the risk of major adverse cardiac events (MACEs), such as death from any cause, cardiac rehospitalization, and stroke. The proportion of MACE-free survival was lower in the CFS ≥ 4 group (log-rank $P<0.001$). After adjusting for confounders, the CFS (each 1-grade increase) was found to be an independent significant predictor of MACE. CFS was shown to predict MACE in patients with ST-segment–elevation MI (STEMI); thus, using it to risk stratify such patients may improve clinical outcomes. These studies highlight several important points; first, a universal definition for frailty in patients with cardiac conditions remains necessary. The

timing at which to perform a frailty assessment and how to use this assessment to appropriately manage elderly patients with ACS remain to be elucidated.¹⁵

There remains a need for randomized clinical trials and international guidelines for the management of ACS in frail elderly patients. The IFFANIAM (Impact of Frailty and Functional Status on Outcomes in Elderly Patients With ST-Segment–Elevation Myocardial Infarction Undergoing Primary Angioplasty): Rationale and Design is studying patients aged >75 years with STEMI at admission, specifically assessing baseline functional status (Barthel index and Lawton-Brody index), frailty (Fried criteria and FRAIL scale [fatigue, resistance, ambulation, illnesses, and loss of weight]), comorbidities (Charlson index), nutritional status (Mini Nutritional Assessment–Short Form), and quality of life (Seattle Angina Questionnaire). The primary outcome the authors plan to assess includes 1-year mortality and its cause.¹⁷ The MOSCA-FRAIL (Invasive Versus Conservative Strategy in Frail Patients with NSTEMI) trial is currently comparing invasive and conservative strategies in elderly frail patients with NSTEMI.¹⁸

Major take-home points:

1. Frailty has been shown to be associated with an increased risk of mortality, longer hospital stay, increased use of resources, and higher risk of delirium.
2. In the United States, frailty is common in patients hospitalized with acute MI, conferring a higher mortality risk that increases with age. PCI in this more frail, older group still confers a strong survival benefit.
3. Frailty risk stratification scores, such as the Clinical Frailty Scale, have been shown to be independent predictors of mortality after STEMI; thus, their use to risk stratify such patients may improve clinical outcomes.
4. Recent studies have not shown a difference in the rate of procedural and in-hospital complications to be significantly different between frail and nonfrail older patients, indicating that frail patients can safely undergo PCI with similar complication rates to nonfrail patients.
5. Cardiologists should think about frailty when assessing elderly patients with ACS; timing before revascularization or valvular procedures is particularly important.
6. There is an unmet need for randomized clinical trials to guide the application of frailty assessment in older adults with cardiac disease.

Primary PCI for STEMI in Older Adults

STEMIs can present with atypical symptoms, especially in older adults, leading to higher likelihood of death and mechanical complications in this age group. The presentation of older patients with STEMI can be different compared with younger individuals with STEMI; for instance, nearly 20% of patients aged

>85 years with STEMI are admitted with a non-ACS-related diagnosis. This occurs in <5% of patients with STEMI who are aged <65 years. Also, older adults tend to have abnormal baseline ECGs and present with atypical symptoms, which makes interpretations of new ECG changes challenging.

Timely PCI has now been established to be a superior strategy compared with fibrinolytic therapy in regard to survival and composite outcome measures.¹⁹ In a study of the AMIS (Acute Myocardial Infarction in Switzerland) registry that stratified patients by age and sex, of a total of 4723 patients with acute MI between 2005 and 2010, 28% were women and 54% were aged >65 years. Elderly patients and women were at increased risk of being withheld PCI when compared with men aged <65 years. Furthermore, there was an increased risk of a delay in door-to-balloon time >90 minutes found in elderly patients. These results suggest that there is discrimination of elderly patients and women in receiving timely PCI.²⁰ According to the Western Denmark Registry, a total of 1322 elderly people (1213 octogenarians and 109 nonagenarians), accounting for nearly 11.6% of the total population with STEMI, were treated with primary PCI between 2002 and 2009. The number of octogenarians with STEMI treated with primary PCI doubled from 2002 to 2009; however, the proportion of nonagenarians did not change. For octogenarians compared with nonagenarians, 30-day mortality was 17.2% versus 25.8% (log-rank $P=0.028$), 1-year mortality was 27.6% versus 32.5% (log-rank $P=0.18$), and 5-year mortality was 53.6% versus 57.3% (log-rank $P=0.087$), respectively. Thus, although nonagenarians had the highest rates of short- and long-term mortality, the 5-year survival was similar and >40% in both groups.²¹

Low or no inclusion of older adults in most ACS clinical trials limits the knowledge on how to make the best decision for the care of patients of this age group when they present with different forms of ACS. For instance, the inclusion of older adults (aged >75 years) has been low, $\approx 14\%$ in VIGOUR (Virtual Coordinating Center for Global Collaborative Cardiovascular Research) trials, such as GUSTO-1 (Global Utilization of t-PA [Tissue-Type Plasminogen Activator] and Streptokinase for Occluded Coronary Arteries) and ASSENT-2 (Assessment of the Safety and Efficacy of a New Thrombolytic).^{4,22} Therefore, there is a need to address the significant discrepancy between the high burden of disease in older adults and the low inclusion rates of this population in large-scale clinical trials.

The prevalence of older adults undergoing primary PCI, although may not still be as high as it should be widely, is increasing, especially in many tertiary centers. For instance, Claessen et al²³ published a 10-year single-center experience in performing primary PCI in patients with acute STEMI, comparing those aged 80 years with younger subgroups, finding an increasing proportion of octogenarians treated with primary PCI from 1997 (3.5%) to 2007 (8.8%). This increase

likely reflects increasing comfort in performing PCI in the elderly population because of improved equipment and technique. In the same study, when outcomes of 30-day and 1-year mortality were compared between the 379 patients aged ≥ 80 years and subgroups of younger patients, the investigators found that age was a significant predictor of short- and long-term mortality (28% 1-year mortality in octogenarians versus 9% in individuals aged <80 years).²³ This is in keeping with the conclusions made by prior trials, including the GISSI-2 (Gruppo Italiano per lo Studio Della Sopravvivenza nell'Infarto Miocardico-2) and GUSTO-1, demonstrating that age is a significant prognostic risk factor after STEMI.^{24,25} However, this study lacked a randomly selected comparison group. Furthermore, sentinel randomized control trials, such as PAMI-1 (Primary Angioplasty in Myocardial Infarction-1) and DANAMI-2 (Danish Trial in Acute Myocardial Infarction-2), that were instrumental in proving that PCI was superior to fibrinolytics had subgroup analyses of the elderly patients (>65 and >70 years, respectively).^{16,17} Although subgroup analyses should be examined with caution, the results of both trials suggested that the elderly patients stand to have improved composite outcomes, including lower rates of mortality and MI, when treated with PCI as opposed to fibrinolytics.^{26,27} Hence, it is likely that older patients with STEMIs who were declined to receive primary PCI and received medical therapy alone, with or without fibrinolytics, had much higher mortality rate than the ones who underwent primary PCI. Another consideration is rescue PCI. Indeed, the REACT (Rescue Angioplasty Versus Conservative Treatment of Repeat Thrombolysis) trial showed that rescue PCI was beneficial in moderate- to high-risk patients who had failed reperfusion with fibrinolytics. The American College of Cardiology and American Heart Association have recommended rescue PCI in the patients treated with fibrinolytics who are considered high risk, such as those aged ≥ 75 years (class IIa).^{28,29}

In summary, elderly patients should not be denied revascularization solely because of age when large-scale clinical trials and evidence-based guidelines recommend PCI for high-risk circumstances.

Major take-home points:

1. The presentation of STEMI in elderly individuals can be different compared with younger individuals with STEMI, with older adults tending to have abnormal baseline ECGs and atypical symptoms.
2. Studies have shown that elderly patients are more likely to receive late treatment secondary to the preconceived notion of frailty and presentation with pain attributable to a multifactorial cause.
3. Multiple studies have shown that the use of invasive cardiac procedures offered to older patients decreases as the patients grow older, which is concerning in light of the

higher-risk features, such as heart failure, diabetes mellitus, and higher GRACE scores, in the elderly patients.

PCI for Older Adults With Cardiogenic Shock Caused by ACS

There has been a paucity of studies reporting on clinical outcomes in elderly patients with cardiogenic shock (CS) in the setting of ACSs. On the basis of the outcomes of the older subgroup of the SHOCK (Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock) trial, patients who were aged ≥ 75 years did not benefit from early revascularization and may have been harmed; and their mortality rate at 30 days was 75%. However, as stated by the SHOCK trial investigators, the low representation of older adults in this trial ($< 20\%$) limits the applicability of this subset analysis from a select patient population enrolled in a randomized trial to the general population.³⁰ The overall results of the SHOCK trial can serve as a guideline in the management of CS complicating MI; however, the SHOCK trial has several limitations. For instance, there were 1992 patients with shock who were screened for the trial but only 302 were enrolled. Therefore, the trial largely represented a selected, relatively healthy subgroup of CS patients, as demonstrated by worse outcomes of screened patients who were not enrolled. It should be recognized that only 152 patients were assigned to an early revascularization arm, of whom only 24 were considered elderly patients, and of whom 20% did not undergo PCI.³¹ The SHOCK trial highlights the need for improved inclusion rates of elderly patients in large-scale clinical trials involving PCI to safely apply the results to patients with MI who experience complications, such as CS. Indeed, observational studies have demonstrated that patients aged ≥ 75 years usually constituted more than one third of all patients with CS.³² It has been shown in study done by Lim et al³³ that despite increased high-risk comorbidities in patients with CS in the setting of ACS, when compared with younger patients, age > 75 years was not shown to be a significant predictor of in-hospital mortality. In fact, in this study, the survival rates of the elderly patients in hospital and at 1 year were not significantly different from survival rates in the younger group. There were also no significant differences based on age group at 30 days or 1 year for MACE, MI, target lesion revascularization, and target vessel revascularization rates in this study. The results suggest that the 1-year survival of elderly patients with acute MI complicated by CS undergoing PCI using contemporary techniques was comparable with the survival rates of younger patients and, therefore, elderly patients presenting with shock may benefit from early PCI.³³ In another analysis of age-related differences in outcomes of patients with acute MI complicated CS who underwent PCI, of 280 patients, 104 were aged > 75 years. The PCI success rates were 92% in the elderly group and 97% in the younger patient group

($P=0.062$). The 6-month mortality rates were 56% in the elderly group and 26% in the younger patient group ($P<0.001$). When a multivariate analysis was performed, the variables independently related to the risk of 1-year mortality in the elderly group were age (hazard ratio [HR], 1.07; 95% CI, 1.02–1.12; $P=0.005$) and PCI failure (HR, 4.01; 95% CI, 1.53–10.51; $P=0.005$). Although age was found to be a strong predictor of mortality, outcome after successful PCI in this study was better than what has been previously reported. On the basis of these data, a strategy of emergency PCI in elderly patients who present with shock and MI remains feasible.³⁴ Certainly, it is also important to recognize that there are studies showing that cardiovascular outcome, especially mortality, can correlate with higher age. For example, in a study assessing the impact of an emergency PCI on 6-month outcomes in patients aged > 75 years with acute MI complicated by CS attributable to predominant ventricular failure, the mortality rate was 51% in the elderly group and 25% in the younger patient group ($P<0.001$). After multivariate analysis, variables related to mortality were found to be primary PCI failure (OR, 4.941; 95% CI, 2.206–11.067; $P<0.001$) and multivessel coronary disease (OR, 1.803; 95% CI, 1.042–3.118; $P=0.035$).³⁵ In another study to determine the characteristics and hospital mortality for elderly patients in CS undergoing emergent PCI, over a decade, 310 of 52 418 patients had PCI for CS, with 24% being elderly patients. In this study, mortality rate for elderly patients with shock who underwent PCI was 46%.³⁶

As proportion of older patients with acute MI increases, shown in several studies, such as the ones presented in Table 1, cardiologists will be managing a greater number of elderly patients; and although having a benefits and risk discussion with patients about management is crucial to make the best decision for each patient, they should remain cognizant that there are data demonstrating that coronary angiography and subsequent needed intervention can be safely and effectively performed in the geriatric population.^{33,34}

In summary, dedicated trials are needed to inform better selection of older patients who can benefit from an early invasive strategy after an acute MI with or without CS. In fact, on the basis of the current data, we believe that although age by itself remains an important outcome predictor in elderly patients, the higher mortality in elderly patients should not discourage the emergency revascularization strategy because patients of this age group can also have the highest magnitude of benefit from an early invasive approach.

Major take-home point:

Age, itself, remains an important outcome predictor in elderly patients, but higher mortality in elderly patients should not discourage the emergency revascularization strategy because many data suggest that the magnitude treatment benefit is directly related to the risk of death.

Table 1. Several Studies Have Shown an Increase in Proportion of Older Patients With Acute MI With and Without CS

| Study | Population | Main Findings |
|--|---|--|
| AMIS registry ²⁰ | 4723 Patients with acute MI between 2005 and 2010, 54% aged >65 y | Elderly patients, especially older women, are at highest risk of being withheld PCI Higher door-to-balloon time in elderly patients, especially older women, vs younger group |
| Western Denmark Registry ²¹ | 11.6% of total patients with STEMI were aged >80 y | More percentage of octogenarians with STEMI received primary PCI in 2009 than in 2002 |
| Claessen et al ²³ | 379 Octogenarians (8.4% of 4506), consecutive and unselected patients, were treated with primary PCI for STEMI at University of Amsterdam between 1997 and 2007 | Annually, the proportion of octogenarians increased Octogenarians had higher mortality rate at 30 d, 30 d to 1 y, and after 1 y compared with younger age groups |
| Lim et al ³³ | From 143 consecutive patients presenting with MI and CS who underwent PCI from the MIG registry between 2004 and 2007, 31.5% were aged >75 y | 1-y Survival of elderly patients with acute MI complicated by CS and undergoing PCI was comparable to younger patients |

AMIS indicates Acute Myocardial Infarction in Switzerland; CS, cardiogenic shock; MI, myocardial infarction; MIG, Melbourne Interventional Group; PCI, percutaneous coronary intervention; STEMI, ST-segment–elevation MI.

PCI for NSTEMI and Unstable Angina in Older Adults

In patients with non–ST-segment–elevation ACS (NSTEMI-ACS), the American Heart Association and American College of Cardiology guidelines recommend guideline-directed medical therapy and, if possible, an early invasive strategy and revascularization if indicated (level of evidence: A).³⁷ The median age of patients in NSTEMI-ACS trials is 65 years, as demonstrated in a recent analysis of the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines Quality Improvement Initiative.^{4,38} However, most trials have excluded older patients; thus, this group of patients continues to be underrepresented in clinical trials.^{4,39} There remains a significant discrepancy between the age of elderly patients enrolled in clinical trials and those in the community, and this gap even gets wider for the very old groups; for instance, patients aged >85 years make up only 2% of trial populations but nearly 11% of the community population.⁴ The risk factor profile of older patients enrolled in trials also differs from the elderly patients living in the community; for example, the elderly patients enrolled in trials have lower rates of classic CAD risk factors and less renal insufficiency.^{4,38} This makes generalizability and the application of evidence-based medicine to individualize care to the patients with NSTEMI-ACS to be difficult.

Multiple studies have shown that the use of invasive cardiac procedures offered to older patients decreases as the patients grow older, which is concerning in light of the higher risk features, such as heart failure, diabetes mellitus, and higher GRACE scores, in the elderly patients. In the GRACE registry, 16% of 18 466 patients were octogenarians and, overall, the study demonstrated lower rates of heart failure, recurrent ischemia, major bleeding, and death among the very

elderly patients who received revascularization compared with the ones who received medical therapy alone. Revascularization was found to be highly beneficial in terms of the primary combined end point of stroke at 6 months, death, and MI in the young, old, and very old, with an associated reduction in mortality at 6 months. These benefits were noted without an undesirable concomitant increase in risk of stroke.⁴⁰

The 2 main contemporary risk scores that have been used to assess the risk of ACS in elderly patients include the GRACE risk score and the TIMI risk score. The GRACE and PURSUIT (The Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy) trial scores have been shown to be superior to the TIMI score in predicting in-hospital mortality (C-statistics, 0.81 versus 0.80 versus 0.68, respectively; $P < 0.001$) and 1-year mortality (C-statistics, 0.79 versus 0.77 versus 0.69, respectively; $P < 0.0001$).^{41–43} The GRACE2 study had 24% of patients who were aged >75 years, in whom it was found that hospital mortality rates increased with age.⁴⁴ In a study including the elderly population, which assessed the in-hospital and 6-month clinical outcomes of invasive versus conservative strategies in 118 patients with STEMI and 40 patients with NSTEMI, the GRACE score was found to be predictive of in-hospital mortality.⁴⁵ In another study that evaluated scores (such as the GRACE score, the Euroscore, the AMIS registry score, and the SYNTAX [The Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery] Trial score) in patients aged >75 years presenting with ACS treated with PCI, 30-day mortality was higher in the upper tertile when compared with the aggregate lower/mid tertiles in all scores, including the GRACE score (40% versus 4%, respectively; OR, 17; 95% CI, 4–64; $P < 0.001$; area under the curve, 0.80), indicating accurate prediction of mortality.⁴⁶ Although the GRACE score is a well-validated scoring system, there have been concerns brought up about its overestimation of risk. An

observational, multicenter, and prospective registry demonstrated that among 156 patients with GRACE score >140, mortality at 6 months was found to be 3.2%; and in dead patients, the mean GRACE index was 147. However, among surviving patients, the mean GRACE index was 163, suggesting that the GRACE score perhaps overestimates mortality risk in ACS.^{47,48}

In a study investigating the in-hospital and 6-month clinical outcomes of invasive versus conservative therapy in patients with STEMI and NSTEMI, the GRACE score was predictive of in-hospital mortality. Furthermore, The Italian Elderly ACS study sought to evaluate an early aggressive (coronary angiography and revascularization in 72 hours, when indicated) versus conservative approach in 313 patients aged >75 years with NSTEMI. The primary outcome of the composite of death, MI, disabling stroke, rehospitalization attributable to cardiovascular reasons, or severe bleeding within 1 year occurred in 43 patients (27.9%) in the invasive group and 55 patients (34.6%) in the conservative group (HR, 0.80; 95% CI, 0.53–1.19; $P=0.26$). The rates of mortality (HR, 0.87; 95% CI, 0.49–1.56), MI (HR, 0.67; 95% CI, 0.33–1.36), and repeated hospital stay (HR, 0.81; 95% CI, 0.45–1.46) did not differ between groups. In those with elevated troponin on admission, the primary end point was significantly reduced (HR, 0.43; 95% CI, 0.23–0.80) compared with those with normal troponin (HR, 1.67; 95% CI, 0.75–3.70; P for interaction=0.03). The early invasive approach did not demonstrate clear benefit compared with conservative management in the studied population; thus, it is not possible to draw definite conclusions about the management of NSTEMI in elderly patients based on the results of this study. Although the study was underpowered, which possibly did not allow for a difference in clinical outcomes, there were numerically lower adverse events in the invasive group compared with the conservative group. Because of higher use of radial access and lower use of glycoprotein IIb/IIIa inhibitors, there were lower rates of bleeding.⁴⁹ The After Eighty Study (Invasive versus conservative strategy in patients aged 80 years or older with non-ST-elevation myocardial infarction or unstable angina pectoris: an open-label randomized controlled trial) also sought to determine whether patients aged ≥ 80 years would benefit from an early invasive strategy or a conservative strategy. The primary outcome of a composite of urgent revascularization, stroke, and death occurred in 40.6% of patients in the invasive group and 61.4% of patients in the conservative group (HR, 0.53; 95% CI, 0.41–0.69; $P=0.0001$). In this study, the invasive strategy was found to be superior to the conservative strategy in reduction of the primary end point.⁵⁰ These findings have been consistent with prior meta-analyses on the topic. When weighing benefits and risks while discussing the option of PCI with an elderly patient, the magnitude of treatment benefit is directly correlated with the risk of mortality.

Receiving early invasive as opposed to ischemia-driven approach, in which a positive noninvasive test is needed before consideration of invasive angiography and revascularization, has been shown to improve outcomes in elderly patients with NSTEMI-ACS. For instance, according to Bach et al, patients aged >75 years treated with an early invasive approach had lower risk of death or MI at 6 months (OR, 0.44; $P=0.02$) compared with delayed or conservative strategy.⁵¹ In TACTICS (Treat Angina With Aggrastat and Determine Cost of Therapy With an Invasive or Conservative Strategy) TIMI 18 trial in patients aged >65 years, researchers have shown an early invasive strategy compared with conservative strategy can yield as high as $\approx 40\%$ reduction in death and MI at 6 months. Interestingly, in patients aged >75 years, this benefit was even higher, at 56% reduction rate. In patients managed conservatively, absolute risk of death or nonfatal MI in patients aged >75 years was 4 times that of patients aged ≤ 55 years (21.6% versus 4.8%, respectively). It is important to recognize that as age increased, an early invasive strategy showed a progressively higher efficacy advantage in absolute and relative risk reductions for death or nonfatal MI. It has been shown that in patients aged >75 years, the early invasive strategy compared with conservative management led to an absolute reduction of 10.8 percentage points (10.8% versus 21.6%; $P=0.016$), with a relative reduction of 56% in death/nonfatal MI at 6 months. The relative reduction at 6 months in nonfatal MI was >70%.⁵¹ In a study of patients aged >85 years undergoing PCI over a 4-year observational period, a total of 180 patients (61.2%) had ACS, including unstable angina or NSTEMI. The 30-day (5.6% versus 3.4%; $P=0.24$) and 1-year (20.0% versus 14.0%; $P=0.19$) mortality rates were similar between the ACS and elective patients, respectively.⁵² In the GRACE study, there were lower rates of heart failure, recurrent ischemia, major bleeding, and death among the very elderly given revascularization compared with medical management. In TACTICS TIMI 18 trial in patients aged >65 years, researchers have shown an early invasive strategy compared with conservative strategy can yield as high as $\approx 40\%$ reduction in death and MI at 6 months. Furthermore, in the FRISC-2 (Fragmin and Fast Revascularization During Instability in Coronary Artery Disease2) study, which included patients aged >65 years, the 5-year mortality was 9.7% in the invasive group compared with 10.1% in the noninvasive group (HR, 0.95; CI, 0.75–1.21; $P=0.693$). The rate of MI was 12.9% in the invasive versus 17.7% in the noninvasive group (HR, 0.73; CI, 0.60–0.89; $P=0.002$). The benefit of the invasive strategy was greatest in male patients, nonsmokers, and patients with ≥ 2 risk factors.⁵³ These studies are in line for others for NSTEMI, demonstrating that PCI is a safe treatment for very elderly patients and has good 1-year survival rates. There remains a need for large-scale studies that include the very elderly to guide interventional cardiologists in treating this growing, challenging cohort.

It remains unclear whether elderly patients derive a greater survival benefit from coronary artery bypass grafting (CABG) or PCI, as large randomized trials have been conducted in lower-risk patients and often exclude elderly patients. It is unclear whether the results of these trials can be extrapolated to elderly patients. Much of the evidence for the elderly patients currently stems from observational, single-center, with small population studies and intermediate follow-up. In a recent study that investigated the effectiveness of CABG and PCI in a large cohort of octogenarians, there were no significant differences between CABG and PCI in 30-day mortality rates in the overall population (5.1% for PCI and 3.6% for CABG; $P=0.23$). For patients aged 80 to 85 years, previous MI, heart failure, chronic renal failure, peripheral vascular disease, and CABG more clearly decreased the risk of death compared with PCI, with no difference in rates of stroke between the 2 strategies. When accounting for coronary anatomical complexity, CABG yielded better results for mortality only in cases of 3-vessel disease associated with the left main coronary artery.⁵⁴ The decision to proceed with medical therapy, PCI, or CABG in the elderly population requires a diligent review of benefits and risks for each patient. In the APPROACH (Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease) study, the interventional approach was found to be superior to medical therapy, with patients aged >80 years having the highest benefit (survival improvement of 17.0% for CABG and 11.3% for PCI). This study did not quantify frailty and quality of life, complex variables that can have profound impacts on morbidity and mortality.⁵⁵

In summary, although elderly patients have higher prevalence of comorbidities to consider prior an invasive strategy for NSTEMI-ACS, such as higher risks of bleeding complications, the risk of ischemic complications from withholding PCI is not trivial. In contrast, elderly patients treated with an invasive strategy have shown in many studies to have higher mortality benefit compared with those with a noninvasive strategy. To safely risk stratify patients, measures often not included in clinical trials need to be strongly considered, including social history, baseline functional status, and frailty.

Major take-home point:

Early invasive approach is a safe treatment strategy in most elderly patients with NSTEMI-ACS, resulting in positive clinical outcomes, such as lower rates of death and MI.

Type of Approach and Stent: Should They Be Different for Older Adults?

Older age has been used as a factor to decide on stent type, as reported in some studies. For instance, in a study analyzing temporal, geographic, and sociodemographic factors

associated with use of drug-eluting stents (DESs) in patients undergoing primary PCI for STEMI, after adjusting for clinical variables, older age was associated with a decreased use of DESs compared with bare metal stents (BMSs).⁵⁶ However, in the XIMA (Xience or Vision Stents for the Management of Angina in the Elderly) trial comparing DESs with BMSs, it was shown that octogenarians have similar procedural success as the younger patients; the rate of all-cause mortality, MI (4.3% versus 8.7%; $P=0.01$), and target vessel revascularization (2.0% versus 7%; $P=0.001$) was significantly lower in DES versus the BMS group. The incidence of major bleeding events did not increase despite longer use of dual antiplatelet therapy in the DES-treated group versus the BMS group.⁵⁷ In the SENIOR (Drug-Eluting Stents in Elderly Patients With Coronary Artery Disease) trial, outcomes were compared in 1200 patients aged >75 years who received DESs and BMSs for stable angina, silent ischemia, or ACS. The primary outcome of major adverse cardiac and cerebrovascular events (composite of all-cause mortality, MI, stroke, or ischemia-driven target revascularization) was compared between the DES and BMS group in an intention-to-treat population at 30 days, 180 days, and 1 year. The primary outcome occurred in 12% of patients in the DES group and 16% of patients in the BMS group (relative risk, 0.71; 95% CI, 0.52–0.94; $P=0.02$). Both groups infrequently experienced bleeding complications (5% DES versus 5% BMS; RR, 0.90; 95% CI, 0.51–1.54; $P=0.68$) and stent thrombosis (1% DES versus 1% BMS; RR, 0.38; 95% CI, 0.00–1.48; $P=0.13$) at 1 year.⁵⁸ Therefore, on the basis of the current limited data, among elderly patients who have PCI, a DES and short duration of dual antiplatelet therapy have been shown to be better than BMS and a short duration of dual antiplatelet therapy in regard to all-cause mortality, MI, stroke, and ischemia-driven target lesion revascularization.

Previous studies have demonstrated that radial artery access decreases the risk of vascular and bleeding complications associated with PCI; however, the radial approach can be more challenging in elderly patients with alterations in vascular anatomical characteristics. In a study of patients aged >70 years, those who underwent a transradial approach had lower rates of in-hospital mortality (0.9% versus 5.6%; $P=0.06$) and nonfatal infarction (0% versus 3.7%; $P=0.05$) compared with those who underwent a transfemoral approach. The rates of major bleeding by the Acute Catheterization and Urgent Intervention Triage Strategy criteria and minor bleeding by the TIMI criteria were lower in patients undergoing the transradial approach compared with those who underwent the transfemoral approach (0% versus 5.6% [$P=0.01$] and 0% versus 7.4% [$P<0.01$], respectively).⁵⁹ In another study of 400 patients aged >75 years with known suspected CAD, the rate of bleeding requiring surgery or transfusion and stroke was 0% in the transradial

approach and 3.2% in the transfemoral approach.⁶⁰ Thus, in elderly patients, a transradial approach seems to have a higher technical success rate and lower complication rates compared with the transfemoral approach.

Major take-home points:

1. Older age alone should not be used as a sole reason to choose BMSs over DESs.
2. In elderly patients, a transradial approach to PCI has a higher technical success rate despite the often complex anatomical characteristics and a lower rate of complications compared with the transfemoral approach.

Pharmacotherapy for ACS in Older Adults

There is no strong evidence on the safety and efficacy of various medical therapy options and combinations in older patients with ACS. Given the fact that the elderly population is more likely to experience adverse effects, such as bradycardia, hypotension, and higher rates of toxicity with drugs, caution should be exercised with initial dosing and up titration to prevent or minimize the development of adverse effects. Age-related declines in liver and kidney function increase drug interactions and frailty, which can pose dilemmas with dosing antiplatelets and anticoagulants in elderly patients. Older age is also classically associated with substantially increased long-term cardiovascular risk and bleeding in patients with medically managed ACS. Pertinent to revascularization dilemmas in older adults, the choice of P2Y12 inhibitor for this age group is not specifically addressed by dedicated clinical trials. However, on the basis of subgroup analysis of trials comparing ticagrelor or prasugrel with clopidogrel, the use of clopidogrel in older patients is generally associated with better overall outcome.⁶¹

Major take-home point:

Data on safety and efficacy of most common medications used for medical management of ACS in older patients are limited. Clopidogrel appears to be the best P2Y12 inhibitor for older patients with ACS on the basis of the available data.

Coexistence of Severe CAD With Severe Aortic Stenosis: Treatment Options in the New Era

CAD is the most common comorbidity influencing outcomes after aortic valve replacement.^{62–65} In fact, in patients who are found to have severe aortic stenosis (AS), CAD is often found incidentally with underappreciated survival implications. Compared with patients who have AS alone, those who have concomitant CAD are more likely to be symptomatic, to be hypertensive, and to have a lower ejection fraction and greater atherosclerotic burden. In both groups, patients who

were elderly and more symptomatic tended to have worse outcomes. These findings suggest that elderly patients with AS and risk factors for CAD should be investigated for atherosclerosis before evaluation for an aortic valve replacement. The current guidelines recommend bypassing significant stenoses at the time of surgical aortic valve replacement.⁶⁶ Those with advanced comorbidities and/or frailty may be better served with medical management alone.⁶⁷ The option that is now becoming more common for treating severe AS is TAVR. When evaluating elderly patients with CAD for TAVR, the following should come under consideration: hemodynamic changes during TAVR in the presence of unrevascularized significant CAD specifically during rapid ventricular pacing and balloon inflation during TAVR, degree of need for revascularization on the basis of the level of CAD and evidence of ischemia if available, the feasible option(s) for revascularization (PCI or surgical), the safety of performing PCI in patients with severe AS, the timing of PCI in regard to TAVR, and the type of stent and antiplatelet regimen.⁶⁶

Cardiac surgeries in patients aged >80 years associate with significant mortality and morbidities. In a study of 600 patients aged >80 years undergoing cardiac surgeries, rates of hospital death, stroke, and prolonged stay (>14 days) were as follows: for CABG: 17 (5.8%), 23 (7.9%), and 91 (31.2%), respectively; for aortic valve replacement (AVR): 8 (7.6%), 1 (1.0%), and 31 (29.5%), respectively; and for AVR+CABG: 7 (6.3%), 12 (10.8%), and 57 (51.4%), respectively. However, percutaneous aortic valve replacement, coronary angiography, and stent deployment have been performed in octogenarians with low complication rates and reasonably good outcomes with the use of standard angiographic catheters and techniques.⁶⁸ In a study assessing the impact of CAD in elderly patients undergoing TAVR, patients with CAD were no more likely to develop major adverse cardiovascular and cerebrovascular events within 12 months of the procedure than those who did not have it (CAD group versus no-CAD group, 15.7% versus 18.3%; HR, 0.76; 95% CI, 0.42–1.36; $P=0.353$). The results of this study suggest that in older patients, concomitant CAD should not be a contraindication to TAVR, as it did not impact outcome status after procedure or incidence of major adverse cardiovascular and cerebrovascular events and survival in elderly patients undergoing TAVR.⁶⁹ However, the gold standard management of CAD in TAVR remains controversial and is currently under investigation. In a study focusing on the prevalence, management, and immediate clinical impact of CAD, 287 consecutive patients undergoing TAVR were divided into 3 groups: optimal medical therapy, preventative PCI for angiographically significant coronary lesions, and a physiologically guided strategy. The results of this study favored a physiologically guided revascularization; however, we believe that larger studies including

only elderly patients will be necessary to determine long-term clinical impact in this population of patients.⁷⁰

The timing of PCI in relation to TAVR remains largely unclear. In a study by Abdel-Wahab et al, PCI before TAVR in 55 patients (median duration between PCI and TAVR was 10 days) was not associated with worse 30-day and 6-month outcomes compared with 70 patients undergoing TAVR alone.⁷¹ Pasic et al⁷² recommended performing TAVR before PCI during the same procedure, with the rationale being that severe AS is the main lesion and thus treating may improve myocardial perfusion. However, this approach carries the risk of additional contrast dye leading to increase the risk of contrast nephropathy, and delivering needed PCI equipment to the coronaries after valve deployment can be challenging.⁷² Wenaweser et al⁷³ compared the approach of concomitant PCI and TAVR, with PCI being performed first, followed by TAVR in the same procedure, with staged procedure in which TAVR was done at ≈1 month after PCI. They found that there was a statistical nonsignificant trend toward higher incidence of major access-related complications and life-threatening bleeding in the staged PCI and TAVR group compared with concomitant TAVR and PCI.⁷³ In a study of 22 344 patients undergoing TAVR, 97.3% of TAVRs were performed without PCI and 2.7% were performed with PCI; in the latter group, there were significantly higher rates of mortality (10.7% versus 4.6%) and complications: vascular injury necessitating surgery (8.2% versus 4.2%), cardiac (25.4% versus 18.6%), respiratory (24.6% versus 16.1%), and infectious (10.7% versus 3.3%) ($P<0.001$ for all), versus the TAVR group. Hospital stays were longer and costs higher in the group receiving concomitant TAVR and PCI.

This study suggested that perhaps the safer option is to perform staged PCI before TAVR.⁷⁴ The currently ongoing ACTIVATION (Percutaneous Coronary Intervention Prior to Transcatheter Aortic Valve Implantation) trial is randomizing patients with CAD to pre-TAVR PCI and no pre-TAVR PCI, to help answer the question of whether pre-TAVR PCI will improve outcomes after TAVR.⁷⁵ Certainly, with increasing popularity of TAVR for patients with severe AS and the high prevalence of CAD in these patients, more randomized trials, like the ACTIVATION trial, are needed to shed light on how and when to safely treat significant CAD in older patients also requiring TAVR. A summary of the studies on PCI timing in older adults undergoing TAVRs is given in Table 2.

Major take-home points:

1. In the cases of concomitant CAD and severe AS, although large studies are still going on, to date available studies showed better outcome success with a PCI approach, especially if fractional flow reserve guided, before TAVR in these patients compared with medical therapy alone for obstructive CAD or simultaneous PCI and TAVR.
2. Percutaneous aortic valve replacement, coronary angiography, and stent deployment have been performed in octogenarians with low complication rates and reasonably good outcomes with the use of standard angiographic catheters and techniques.
3. Left atrial appendage occlusion has been performed in patients with atrial fibrillation who have contraindication to oral anticoagulants or an elevated bleeding risk, which can be also a consideration in patients undergoing TAVR.

Table 2. PCI Timing in Older Adults Undergoing TAVRs

| Study | Population | Main Findings |
|---------------------------------|---|---|
| Zivelonghi et al ⁷⁰ | 43% of 287 consecutive patients between 2010 and 2016 undergoing TAVR at University of Verona had significant CAD and were divided into medical therapy alone, angiographically guided PCI, and FFR-guided PCI, per operator decision | FFR-guided PCI in the same TAVR procedure was found to have better short-term (at 30 d) clinical outcomes compared with the other 2 strategies |
| Abdel-Wahab et al ⁷¹ | Clinical outcomes of 55 patients with PCI+TAVR and 70 with isolated TAVR, in patients without obstructive CAD, were compared between 2007 and 2011 at Academic Teaching Hospital of the Universities of Kiel and Hamburg | PCI before TAVR appeared feasible and safe without increase of major adverse effects at 30 d or 6 mo |
| Pasic et al ⁷² | Combined elective PCI and TAVR were performed in 46 (11%) patients between 2008 and 2011 at German Heart Center (Berlin, Germany) | Single-stage approach with combined elective PCI and TAVR is feasible and safe |
| Wenaweser et al ⁷³ | Among 256 patients undergoing TAVR, 167 had CAD and 59 underwent either staged (n=23) or concomitant (n=36) PCI | Major clinical outcome at 30 d was similar for patients undergoing isolated TAVR compared with TAVR combined with PCI A nonsignificant trend for higher access-related complications and life-threatening bleeding in staged PCI and TAVR group compared with concomitant TAVR and PCI group |

CAD indicates coronary artery disease; FFR, fractional flow reserve; PCI, percutaneous coronary intervention; TAVR, transcatheter aortic valve replacement.

Conclusions

By the year 2048, given the trend toward increasing life expectancy, the proportion of people aged ≥ 65 years is projected to increase from 12.4% to 19.6% in the United States, with those aged ≥ 85 years expected to nearly double from 9.3 to 19.5 million.⁷⁶ Our review of the literature suggests that there are robust evidence-based guidelines recommending PCI in higher-risk patients, such as elderly patients presenting with ACS; however, it remains underused in this population. Multiple studies have shown that the use of invasive cardiac procedures offered to older patients decreases as the patients grow older, which is concerning given the higher-risk features, such as heart failure, diabetes mellitus, and higher GRACE scores, in the elderly patients. This underuse is despite the fact that patients aged >80 years can have the largest absolute reduction of in-hospital mortality after PCI when presenting with ACS compared with younger age groups.⁴ An early invasive approach is a safe treatment strategy in most elderly patients with ACS and has been shown to significantly improve mortality.

Although time trends have demonstrated a decline in rate of mortality secondary to heart disease over the past 2 decades, the degree of this decrease has been far less for the older compared with younger patients.⁷⁷ Therefore, it is on clinicians to embrace and consider offering both medical and as much as feasible invasive therapies to elderly patients with significant CAD.

The balance between preventing ischemic and bleeding complications leaves the physician with the important task to risk stratify patients, which requires an important understanding of the frailty and cognitive impairment that can affect the elderly patients as well as each individual patient's goals of care, comorbidities, and quality of life.³ In the elderly population, frailty shares many risk factors with ACS, both contributing to decreased physiologic reserve, leading to increased vulnerability. Frail old patients are more likely to be women, to be ethnic minority members, and to have extensive comorbidities. Studies have demonstrated that although PCI is underused in frail older patients, they are still likely to derive a significant survival benefit from intervention. In addition to a mortality benefit, there is also evidence of improved quality of life after PCI when clinically indicated in older patients. Although there are risk stratification scores, such as the Essential Frailty Toolset and the Clinical Frailty score, there remains a need for comprehensive geriatric assessment to be incorporated in classic risk scores, such as GRACE. Presence of concomitant comorbidities, such as severe AS and/or atrial fibrillation, with the need for long-term anticoagulation further poses challenges on deciding the best revascularization strategy in older

patients. Therefore, there is a strong need for greater inclusion and better representation of elderly patients in revascularization clinical trials and expanded registries to monitor the benefits and risks of different revascularization strategies in older adults to inform the best practice for this growing age group.

Disclosures

None.

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