



## Coronary revascularization in the elderly with stable angina

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### Abstract

A proportion of elderly with coronary artery disease is rapidly growing. They have more severe coronary artery disease, therefore, derive more benefit from revascularization and have a greater need for it. The elderly is a heterogeneous group, but compared to the younger cohort, the choice of the optimal revascularization method is much more complicated among them. In recent decades, results has improved dramatically both in surgery and percutaneous coronary intervention (PCI), even in very old persons. Despite the lack of evidence in elderly, it is obvious, that coronary artery bypass surgery (CABG) has a more pronounced effect on long-term survival in price of more strokes, while PCI is certainly less invasive. Age itself is not a criterion for the selection of treatment strategy, but the elderly are often more interested in quality of life and personal independence instead of longevity. This article discusses the factors that influence the choice of the revascularization method in the elderly with stable angina and presents a complex algorithm for making an individual risk-benefit profile. As a consequence the features of CABG and PCI in elderly patients are exposed. Emphasis is centered on the frailty and non-medical factors, including psychosocial, as essential components in making the decision of what strategy to choose. Good communication with the patients and giving them unbiased information is encouraged.

*J Geriatr Cardiol* 2015; 12: 555–568. doi:10.11909/j.issn.1671-5411.2015.05.017

**Keywords:** Angina; Cardiopulmonary bypass; Coronary artery disease; Stents; The elderly

### 1 Introduction

Recently, the segment of the elderly is rapidly growing among those who needed revascularization for stable coronary artery disease.<sup>[1,2]</sup> However, there is no universally adopted definition of “elderly”, but it is believed that it represents the person of 70–75 years and older. This group of patients is heterogeneous, but compared with younger persons, they have more extensive coronary artery disease (CAD) and more comorbidity. There is strong evidence that elderly patients derive more benefit from revascularization, than younger ones.<sup>[3–5]</sup> Despite the fact that the biological age does not correspond to chronological age, this cohort of patients requires more attention in terms of a tailored approach to the risks and benefits of revascularization. In this paper, we will discuss evidence and factors for choosing

revascularization procedure in elderly patients with stable angina.

### 2 Search strategy

For this review, data were identified by searches of PubMed between 1 January 1980 and 1 July 2014 using the following terms: “PCI”, “cardiac surgery”, “CABG”, “coronary artery surgery”, “stable angina”, “coronary revascularization”, “elderly”, “older adults”, and “octogenarians”. Both full-text papers and abstracts were reviewed. Additional papers were identified from personal libraries and the reference lists of retrieved articles.

### 3 Randomized controlled trials

In the old AWESOME trial (The Angina With Extremely Serious Operative Mortality Evaluation) comparing groups undergoing percutaneous coronary intervention (PCI) and coronary artery bypass surgery (CABG), more than 50% of the patients were older than 70 years old. After three years of follow-up, survival in the two groups did not significantly differ (79% in the CABG group and 80% in the PCI group). In the subgroup of patients older than 70 years, in-hospital

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**Received:** November 8, 2014

**Revised:** January 3, 2015

**Accepted:** April 3, 2015

**Published online:** September 20, 2015

mortality was higher in CABG patients. After three years of follow-up, no significant differences in survival were shown, however, the PCI group had a higher incidence of unstable angina and repeat revascularization.<sup>[6]</sup>

Outcomes by age were examined in the BARI (Bypass Angioplasty Revascularization Intervention) trial. It showed that 30-day mortality in patients older than 65 years was higher than in younger ones, and did not differ for CABG and percutaneous transluminal coronary angioplasty (PTCA). Patients in the CABG group had a greater relief of angina and fewer repeat interventions, but more strokes. Five-year survival rate in the elderly was 85.7% for CABG and 81.4% for PTCA; cardiac mortality was higher in the PTCA patients with diabetes mellitus.<sup>[7]</sup>

Pooled analysis of four stent trials [ARTS (Arterial Revascularization Therapies Trial), ERACI II (Second Argentine Randomized Trial of Percutaneous Transluminal Coronary Angioplasty Versus Coronary Artery Bypass Surgery in Multivessel Disease), MASS II (Second Medicine, Angioplasty, or Surgery Trial), and SoS (Stent or Surgery)] confirmed these results.<sup>[8]</sup>

Randomized trials, comparing coronary angioplasty and bare-metal stenting with cardiac surgery, established the evidence basis for the choice of the method of revascularization for a long time. But they have become obsolete. The average age of patients was 60 years, patients with severe comorbidities, total chronic occlusions and severe stenosis of the left main coronary artery were not included. There were no more than 10% of potentially eligible patients participating in trials, most of whom actually had one or two-vessel disease and normal left ventricular ejection fraction. Hence, even if it could be extrapolated to the elderly, it would be relevant only to the healthiest of them.

It's that patient in whom the advantage of CABG compared to PCI in survival, myocardial infarction (MI) and quality of life is less pronounced. Most of all, 8%–10% of patients from the PCI group crossed to CABG.<sup>[9,10]</sup>

However, randomized trials have demonstrated the advantage of CABG in high risk patients in the context of long-term survival and treating angina. It was also shown that the incidence of recurring angina and repeated revascularization was 2–4 times higher in subgroups of patients who underwent PCI.<sup>[9–13]</sup> Large meta-analyses have confirmed these results.<sup>[14–16]</sup>

Significant innovations both in PCI and cardiac surgery as well as in pharmacological accompaniment have taken place in recent decades: drug-eluting stents (DES) markedly reduce the rate of restenosis, and anesthetic and postoperative care in surgery. Nonetheless, in these trials, antiplatelet therapy was received only by 20% of PCI patients, and left internal thoracic arteries, one of the most important predic-

tors of a favorable prognosis after CABG, were used only in 10% of surgery patients.<sup>[17]</sup>

In the middle of the first decade of the 21<sup>st</sup> century, DES have actively been used in clinical practice (up to 30% in some European centers), including patients with multivessel disease and left main disease, despite the fact that in clinical guidelines, CABG was still recommended as first-line therapy.<sup>[18]</sup> The SYNTAX trial clearly defined the indications for PCI and CABG in complex CAD. In patients with multivessel coronary disease after a year of follow-up, no significant difference in the incidence of myocardial infarction and mortality have been reported, but a five-year follow-up showed a higher mortality rate and major adverse cardiac events (MACE) in the PCI group compared with CABG, especially in patients with high SYNTAX-scores.<sup>[19]</sup> The average age was 65 years. There are no contemporary randomized trials comparing DES and CABG in elderly patients.

## 4 Registries

Generalizability of randomized controlled trials (RCT) involving the elderly is limited due to a lack of frail patients. Mostly, they included relatively well-conditioned patients with good cognitive status and long life expectancy. In actual clinical practice, there is a bias on the choice of a given method of treatment. Thus, in the registries, we should expect more patients with frailty and comorbidities, so it will have more implications to physician's reality.

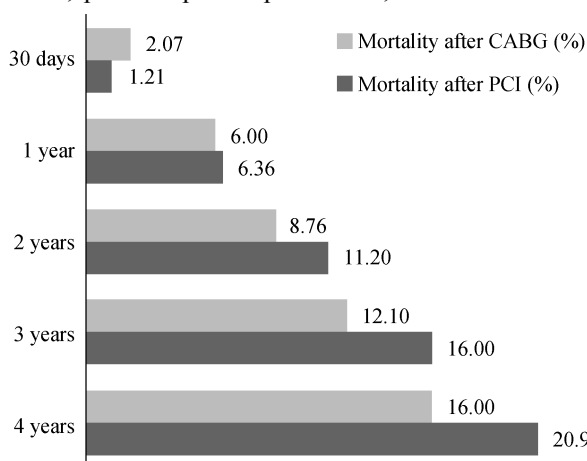
According to the APPROACH (Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease) registry (patients enrollment from 1995 to 1998), which included more than 6000 patients older than 70 years, the survival rate in patients aged 70–79 years was 87.3% in the CABG group *versus* 83.9% in the PCI group; for patients older than 80 years 77.4% in the CABG group *versus* 71.6% in the PCI group. CABG patients had more extensive CAD, PCI patients had more comorbidities.<sup>[4]</sup>

In the BARI-like registry,<sup>[20]</sup> there was a slight survival advantage of the CABG compared with PCI in all patients older than 70 years. Peterson, *et al.*<sup>[21]</sup> included more than 230,000 elderly patients ( $\geq 75$  years) from the registries. PCI patients had less comorbidity; most of them had 1–2 vessel disease, whereas the majority of patients undergoing CABG had 3-vessel disease and more risk factors for cardiovascular disease (CVD). Stents were used in 35%–58% of patients treated with PCI; left internal thoracic artery in 52%–80% with CABG. After adjusting for the impact of potential omitted modifiers, in-hospital mortality was 3.0% of PCI and 5.9% for CABG. This trial also showed a significant reduction in mortality for both procedures for the period from 1991 to 1999.<sup>[21]</sup>

In a large meta-analysis of 66 trials, analyzing revascularization in patients 80–89 years, there also was a trend to a higher 30-day mortality among patients undergoing CABG (7.2% versus 5.4% in the PCI group) and comparable one-year and three-year mortality between the two strategies. After five years, meta-analysis demonstrated a trend towards improved survival in the CABG (68% vs. 62% in PCI).<sup>[22]</sup> Many of the trials included in this meta-analysis were too outdated by current procedures (little use of stents and contemporary innovations of cardiac surgery).

The most recent ASCERT trial included 86,244 CABG patients and 103,549 PCI consecutive patients from the Society of Thoracic Surgeons' database, the American College of Cardiology Foundation database, and Centers for Medicare and Medicaid Services (CMS) records from 2004 to 2008. All included patients were  $\geq 65$  years, had multivessel disease (2 or 3 vessel disease) with stable angina. Primary outcome criterion was all cause mortality. To reduce treatment selection bias, inverse-probability-weighting (IPW) adjustment was made and IPW-adjusted data were used to compare CABG and PCI with similar clinical characteristics. Even in the low risk subgroup [age < 75 years old, no diabetes, glomerular filtration rate (GFR)  $\geq 60$  mL/min, ejection fraction  $\geq 50\%$ ], a long-term advantage of CABG was shown. Mortality after a year of follow-up was approximately the same in both groups. But after four years, Kaplan-Meier survival for PCI was only 79% of the survival measured for CABG (Figure 1). Diabetes, history of smoking, heart failure and peripheral arterial disease were the predictors of CABG advantage.

Limitation of all registries is the physician-patient choice (no randomization). The results may be influenced by the modifier, such as frailty, past surgery, limited ability to walk or care, personal patient preferences, or another. If frailty



**Figure 1. Mortality after CABG and PCI in patients  $\geq 65$  years.**<sup>[23]</sup> CABG: coronary artery bypass surgery; PCI: percutaneous coronary intervention.

was in 10% of CABG patients and in 35% of PCI patients and doubling the risk of mortality, it could explain the mortality differences between two groups.<sup>[23]</sup>

The advantage of CABG may be explained by the fact that there were many patients with more extensive CAD, in which the advantage of CABG has become more obvious; and perhaps most of the frail patients were in the PCI group due to fear of surgery.

In the latest multicenter trial comparing PCI and CABG on more than 3000 patients, where the average age of the patients was 65 years, PCI had markedly higher MACE rates, including mortality after 7 years of follow-up.<sup>[24]</sup> Importantly, the advantage of CABG increased more and more with the length of follow-up. The number of patients with 3-vessel disease was three times higher in CABG group. The long-term survival advantage of CABG was reached at the price of higher incidence of early postoperative strokes (0.1% vs. 0.7%).<sup>[24]</sup>

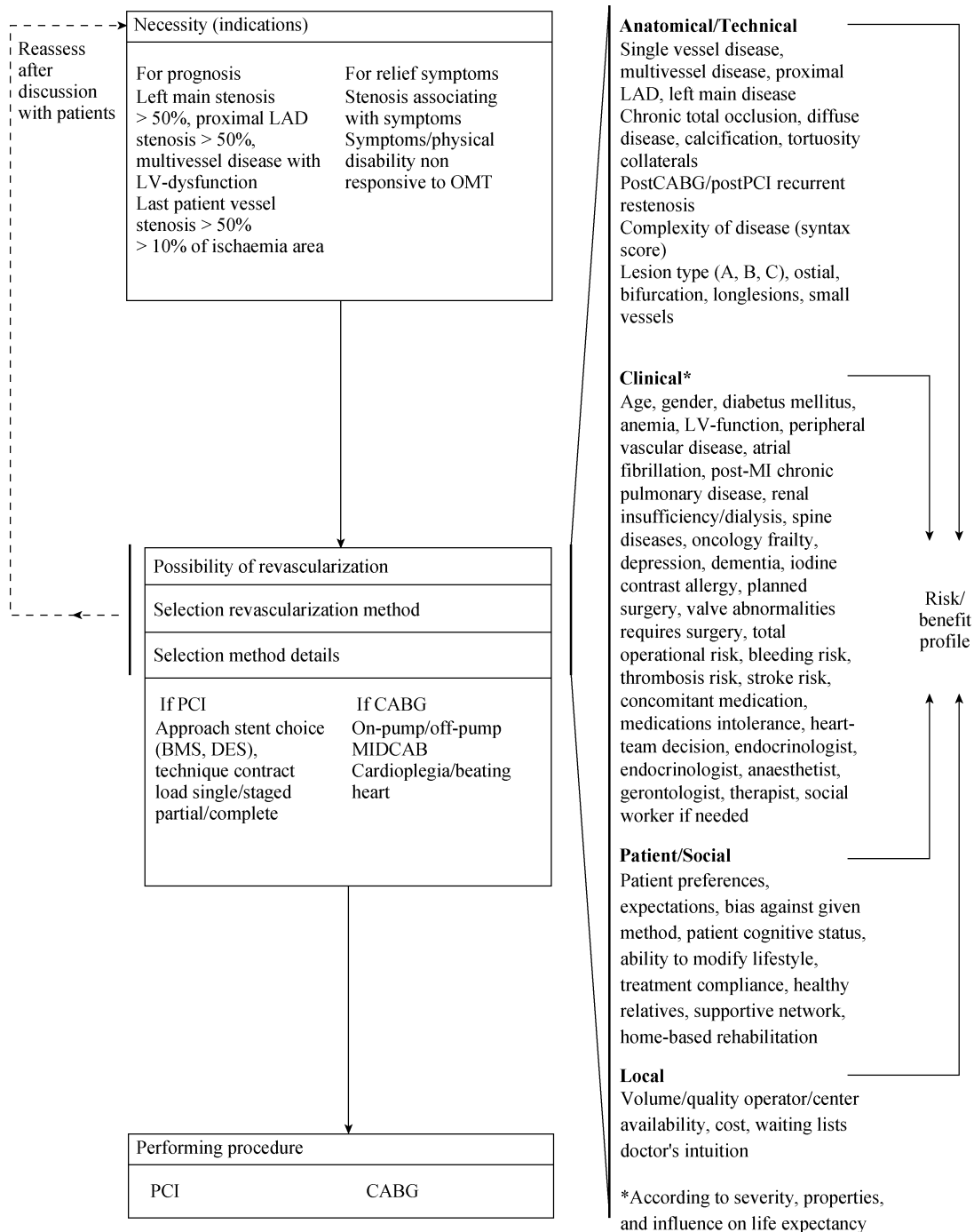
In a recent meta-analysis of registries, comparing DES and CABG in patients  $\geq 75$  years ( $n = 3864$ ), no significant difference in mortality rates were shown as well as the number of strokes and myocardial infarctions between the two strategies during mean follow-up of 18 months. Repeat revascularization rates were significantly higher for patients who received DES. In addition, CABG was associated with lower stroke/MI/mortality rates for patients without chronic obstructive pulmonary disease (COPD) and with more than one factor of the four important risk factors (ejection fraction, COPD, diabetes, and proximal left anterior descending disease with stenosis  $\geq 70\%$ ). No adjustment for frailty, mental and social status was made.<sup>[25]</sup>

Lessons arising from registries are: the more complex the lesion, the greater the benefit of CABG; on the other hand, the more comorbidities, the less the tolerance the CABG. Both CABG and PCI improve survival in elderly with stable angina and multivessel disease, but CABG has a more pronounced and long-term effect at the expense of higher early mortality and strokes.

## 5 Factors for consideration

The risk of complications after both procedures (PCI and CABG) is associated not with chronological age itself, but with the physiological age: the numbers of comorbidities, patient activity, exercise capacity, mental status.

For example, in patients  $\geq 80$  years without risk factors undergoing PCI, mortality was 0.79%, but in the presence of renal failure or ejection fraction less than 35%, mortality was 7.2%.<sup>[26]</sup> To make right choice, physician needs to take into account numerous factors as outlined in Figure 2.



**Figure 2. Algorithm for revascularization method selection.** BMS: bare-metal stent; CABG: coronary artery bypass surgery; DES: drug-eluting stent; MI: myocardial infarction; LAD: left anterior descending artery; LV: left ventricular; MI: myocardial infarction; MID-CAB: minimally invasive direct coronary bypass; OMT: optimal medical therapy; PCI: percutaneous coronary intervention.

**5.1 Anatomical**

As mentioned above, more extensive CAD leads to worsening outcomes after PCI. The percentage of calcification of the coronary arteries significantly increases with age.<sup>[27]</sup> PCI in calcified plaques is often accompanied by

periprocedural complications, and lead to inadequate disclosure of the stent and a large rate of restenosis.<sup>[28]</sup> Performing PCI in the elderly could be limited because of severe tortuosity of the vessels, which makes it difficult to manipulate the catheterization tools.

In a recent meta-analysis comparing PCI and CABG for

left main disease in patients  $\geq 70$  years, 10 trials were studied with a total of 2,386 patients (PCI,  $n = 909$ ; CABG,  $n = 1477$ ). No significant differences were found between PCI and CABG for all cause-mortality, nonfatal myocardial infarction, major adverse cardiac and cerebrovascular events at 30 days as well as at 12 and 22 months. However, PCI was associated with lower rates of stroke at 30 days [odds ratio (OR): 0.14, 95% CI: 0.02–0.76] and 12 months (OR: 0.14, 95% CI: 0.03–0.60) and higher rates of repeat revascularization at 22 months (OR: 4.34, 95% CI: 2.69–7.01). SYNTAX score was not estimated.<sup>[29]</sup>

## 5.2 Diabetes mellitus

In a large meta-analysis, Hlatky, *et al.*<sup>[16]</sup> indicated that 5-year mortality in middle-aged patients with diabetes mellitus and stable multivessel coronary disease undergoing PCI was 20% and 12.3% for CABG. For  $\geq 65$  old patients in the CARDIA trial, comparing PCI (BMS and DES) and CABG in patients with multivessel disease, survival for CABG was higher than for PCI compared with younger patients (HR: 1.48 vs. HR: 1.04). However, the CABG group showed significantly more strokes.<sup>[30]</sup>

According to the SYNTAX trial, the frequency of MACE after 1-year follow-up in patients with diabetes mellitus treated with paclitaxel DES was two times higher than in CABG.<sup>[30]</sup> These data were confirmed for non-elderly patients in two recent major meta-analyses comparing DES and CABG (mean age 63 years). CABG had a more pronounced effect on the survival and decreasing the rate of myocardial infarctions, but stroke risk was significantly lower with DES. The rate of repeat revascularization was much higher in DES patients.<sup>[31,32]</sup> Thus, patients with diabetes mellitus and more severe CAD should undergo CABG, adjusted for the risk of stroke.

There have been no RCT, comparing PCI and CABG in elderly patients with diabetes mellitus.

## 5.3 Chronic kidney disease

Chronic kidney disease (CKD), even with mild severity (the level of GFR 59–30 mL/min), increases the relative risk of morbidity and mortality in both CABG and PCI.<sup>[33–35]</sup> Perioperative mortality after CABG was 1.3% in patients with normal renal function, and 9.3% in patients with severe CKD, and 9% in patients on dialysis.<sup>[36]</sup> CKD also significantly raises the risk of postoperative complications after both surgery and PCI. This is probably due to the continuous ventilation of the lungs, and a higher incidence of bleeding.

The trial on the basis of the registry APPROACH with 8-year follow-up demonstrated that CABG improves out-

comes in patients with chronic renal failure, regardless of severity, and PCI effects were on survival only in patients on dialysis. Outcomes of CABG in patients with CKD not requiring dialysis were significantly better compared to PCI, probably due to the high frequency of restenosis (DES were not used), the low rate of complete revascularization, and acute renal failure after PCI.<sup>[37]</sup>

In a large Duke University Hospital registry ( $n = 4584$ ), PCI improved outcomes in patients with mild to moderate CKD, but not severe CKD. CABG improved outcomes in all groups compared to conservative therapy. The average age of patients with CKD not requiring dialysis in this trial was 72 years. Survival in the CABG group compared with PCI as a whole was significantly better (OR: 0.65,  $P = 0.002$ ).<sup>[38]</sup>

Ashrith, *et al.*<sup>[39]</sup> showed that the risk of postoperative hemodialysis is significantly higher in the CABG group compared with DES-treated patients (OR: 3.2,  $P < 0.001$ ). Long-term survival was better in the CABG group for patients with three-vessel, but not two-vessel disease [hazard ratio (HR): 0.61,  $P = 0.06$  and HR: 1.12,  $P = 0.7$ , respectively].

Comparison of DES and CABG in patients with CKD ( $n = 1069$ ) and multivessel disease, patients with two-vessel disease had no significant difference in the incidence of death (4.1% in the DES group vs. 3.1% in the CABG group,  $P = 0.633$ ), myocardial infarction (4.6% vs. 3.1,  $P = 0.510$ ) and stroke (1.4% vs. 2.1%,  $P = 0.617$ ) and repeat revascularization (6.7% vs. 3.1%,  $P = 0.181$ ) after two years of follow-up. After three years, the rate of repeat revascularization was significantly higher in the DES group (12.5% vs. 4.4%,  $P = 0.001$ ). Age had no effect on the difference in outcomes.<sup>[40]</sup>

A less invasive approach is more justified in the most compromised in terms of comorbidities and frail patients, prevalent among the elderly. PCI could be safely used in patients with CKD to reduce early mortality, however, it is necessary to consider a balance between high risk for bleeding after DES and high risk of restenosis for BMS.<sup>[41]</sup>

## 5.4 Quality of life

The influence of CABG on long-term survival in multivessel disease is strongly evident, but for the elderly the quality of life may be the more important factor when considering the treatment method between two strategies. However, it is not so easy to assess, given that a fully “blind” trial comparing CABG and PCI is not possible, making it difficult to determine what is a placebo-like effect, and what is the real effect of the treatment. Separately, both strategies have shown excellent results in terms of improv-

ing the quality of life in elderly patients compared with medical therapy alone.<sup>[42,43]</sup>

In a subsequent analysis of the TIME trial, patients undergoing CABG experienced greater symptomatic relief and reported improved quality of life at one year in comparison with patients in whom PCI was performed.<sup>[44]</sup> The AP-PROACH registry has shown that elderly patients who revascularized tended to have better quality of life than those treated medically.<sup>[45]</sup> At the same time, high-risk patients and octogenarians in this registry experienced a greater improvement in quality of life from CABG than from PCI, except for exertional capacity. In contrast, another trial assessing the quality of life in octogenarians after optimal medical therapy, reported that PCI and CABG have comparable results between all methods.<sup>[46]</sup>

In general, most trials showed that CABG provides excellent quality of life, but it may be adjusted according to many factors. So among the cohort of elderly who require revascularization, this may not be entirely true for given person.<sup>[47,48]</sup>

As for non-elderly trials, results of SYNTAX showed that after a year of follow-up, CABG provided greater relief of severe angina, but after one month, which is especially important for the elderly, there was significant difference in bodily pain, social and physical functioning in favor of PCI. In the subgroup of patients  $\geq 75$  years after one year of follow-up, no significant difference between the effects on quality of life of PCI and CABG were reached.<sup>[49]</sup>

In the large meta-analysis by Bravata, *et al.*,<sup>[15]</sup> the authors concluded that CABG effectively eliminates angina in one, three and five years of follow-up, compared with BMS-PCI with a difference of 5% to 8% ( $P < 0.001$ ). Similar results were obtained in other trials.<sup>[50-52]</sup>

### 5.5 Neurocognitive function

Significant impact on the quality of life has neurocognitive component. Postoperative cognitive impairment is a well-defined syndrome,<sup>[53]</sup> but it still has no accepted clear definition. There are several reasons for the appearance of cognitive impairment (Table 1) after cardiac surgery. This phenomenon was reported in many trials. However, recent articles claimed to doubt these results, since many of them used not clearly defined terms and had incorrectly assessed neurocognitive status.<sup>[54]</sup> Trials, that directly compared PCI and CABG, showed no significant difference in the incidence of cognitive impairment between the two strategies.<sup>[55]</sup> It was also reported, that due to the presence of atherosclerotic changes in the brain vessels, cognitive impairment in elderly already existed before the procedure, that markedly

**Table 1. Causes for increased risk of cognitive cerebral injury with open heart surgery.<sup>[61]</sup>**

Embolitic deposition to the brain
Blood pressure fluctuations
Non-physiological pulsation during extracorporeal perfusion
Activation of the inflammatory cascade due to blood elements contacting non-endothelialized surfaces
Altered cerebral oxygenation

increases the risk of worsening cognitive status in the post-operative period.<sup>[56-58]</sup>

Other trials have shown that cognitive impairment is related to anesthesia and stress, rather than the operation itself. A week after CABG, cognitive status declined, but after two months returned to normal level and even improved.<sup>[59,60]</sup> At present, the risk of neurocognitive impairment after cardiac surgery has substantially been reduced.<sup>[60]</sup> Theoretically, embolic risk also exists after PCI because of retrograde cannulation through the aorta, but has not been proven in actual practice.<sup>[61]</sup> New trials in elderly, performed in accordance to standardized assessment of neurocognitive status, are strongly needed.

### 5.6 Strokes

Greater incidence of stroke after CABG *versus* PCI was reported in the majority of RCT and registries upon comparing these strategies.<sup>[24,29,31,62-64]</sup> Elderly patients have also experienced more perioperative strokes after CABG compared to PCI: 3.5% vs. 0.4% in the study by Peterson,<sup>[65]</sup> and 2.84% vs. 0.57% ( $P < 0.001$ ) in the study by Dacey.<sup>[43]</sup>

However, the number of strokes after cardiac surgery has decreased dramatically in recent years due to improvements of preoperative management and procedural techniques.<sup>[66]</sup> In a trial of 6323 patients with multivessel and/or left main coronary artery disease, there were no difference in the stroke incidence in the PCI vs. OPCAB (off-pump coronary artery bypass), but not on-pump surgery.<sup>[67]</sup>

Additional research is warranted to determine the risk factors for stroke after CABG, proper diagnostics approaches,<sup>[68]</sup> and the optimal methods performing this invasive procedure, in particular implementing intraoperative epiaortic ultrasound or even not manipulating on the aorta.

### 5.7 Frailty

It is difficult to imagine a discussion about the choice of cardiovascular treatment strategies in the elderly, without discussing frailty. Frailty is defined as increased vulnerability to poor resolution of homeostasis after a stressor event which increases the risk of adverse outcomes.<sup>[69]</sup> It could be

considered as a marker of biological age. Frailty is closely related to mental status. On the other hand, it seriously worsens the clinical course of CAD, which is a serious factor that makes hard decisions as to the treatment method to choose.

We cannot distinguish frail and unfrail patients in all previous RCT and registries, making them hardly applicable to the real world practice,<sup>[70]</sup> where in fact 19% of  $\geq 65$  years patients undergoing PCI are frail and 47% have intermediate frailty.<sup>[71]</sup>

Frailty can be assessed in 5–10 min. Frail older persons can be identified by a set of symptoms, such as weight loss, muscle weakness, fatigue, decrease in the overall activity and slow gait. There is a variety of methods for detecting this condition, however, there is no common scale.<sup>[69]</sup> It seems reasonable to integrate frailty into risk models and/or to establish clear indicators to assess frailty. Adding frailty, comorbidity, and poor quality of life to the Mayo Clinic risk score significantly improved the prediction of cardiac adverse long-term outcomes.<sup>[72]</sup> It is necessary to educate physicians—not only geriatricians—to detect and assess frailty.<sup>[73]</sup>

Frailty worsens outcomes, regardless of age, sex and comorbidities.<sup>[70]</sup> Three-year mortality is up to four times higher (6%–28%) in frail persons *versus* the non-frail after revascularization.<sup>[72]</sup> Nevertheless, both PCI or CABG is widely performed in frail elderly patients.<sup>[72,74]</sup> Importantly, frailty could appear after procedure.<sup>[75]</sup>

Which treatment method to choose in the frail patient, and whether to make an intervention is still a controversy.<sup>[76]</sup> In any case, it is clear that frailty needs to be addressed, as well as frail patients need much more attention, nutritional changes and early postoperative activity.

So, which revascularization procedure is preferable in the frail elderly patient? European revascularization guidelines<sup>[77]</sup> and common sense suggest that outcomes in the frail patient should be better with a less invasive procedure,<sup>[78]</sup> but we need more evidence. Until then, frailty itself is not a reason to refuse major surgery.

### 5.8 Patient preference and advised consent

The patient should have a few days to make a decision after angiography, as well as the opportunity to discuss the situation with relatives, but it's still a controversy whether to perform *ad-hoc* PCI in elderly or not, because of more invasiveness. It is desirable to discuss plans before the Cath lab, so coronary angiography may be not performed at all, if patients firmly refused revascularization.

The patient is entitled to receive complete and accurate, objective, evidence-based information about his condition and perspectives, given in a clear, accessible way to him.

Risks and potential benefits in the short and long-term of optimal medical therapy and revascularization, and expected survival status. The effectiveness of treatment of angina, quality of life, the likelihood of the need for re-intervention should be discussed. Information about the potential neurological complications, and the risk of thrombotic complications, bleeding, technical features of CABG, and the choice of the stent in the case of PCI should be provided.

Also of great importance is not only what information is provided the patient, but how it may be biased, and how the patient understood it in the context of his own interests, i.e., it should be adequate and should be properly reported (Table 2).<sup>[79]</sup> And the lack of sufficient evidence is not an obstacle here,<sup>[80]</sup> but unfortunately, most patients are given a view from one side only. And 70% of those who had undergone PCI, suppose that it improves survival and prevents myocardial infarction.<sup>[80]</sup> At least 15% of all PCI is inappropriate,<sup>[81]</sup> but patients nonetheless are satisfied.<sup>[82]</sup> Physicians overestimate the benefit of PCI and put patients into a bias,<sup>[83–85]</sup> but also the patients themselves often choose PCI because of the expectation of pain after CABG in the early postoperative period, the scar on the chest and neurological complications.<sup>[86]</sup> In real practice, there is a preconception not to perform CABG in elderly person, even in case of little risk of in-hospital mortality, when there exists a possibility to perform PCI.

The quality of life for the elderly is often more important than the longevity, especially the maintenance of independence, but physician still have to ask them. And for plenty of older persons life expectancy can be quite high.<sup>[87]</sup> A heart-team and, in special cases, an endocrinologist and gerontologist as advisers are encouraged.

It should be keep in mind that the patient's opinion may change, so it is essential to reassess.<sup>[88]</sup> And many of them are not willing to risk their life, referring to the risk of cognitive impairment.<sup>[89]</sup>

### 5.9 Psychosocial

In the elderly, non-medical factors are particularly important: support of relatives<sup>[90]</sup> and social services in the postoperative period.<sup>[42]</sup> These aspects are closely related to mental status and have the importance, not only in terms of compliance to medical therapy and especially dual anti-platelet therapy (DAPT), but primarily as a strong factor that directly affects the survival and quality of life. For example, 30%–40% of patients, in whom the CABG was performed, have depression that significantly affects the adverse outcomes.<sup>[91]</sup> Thus, the therapist and gerontologist should assess the so called “mental frailty”, i.e., the will to live, the desire to live. It should be corrected if it is possible, or another option of treatment should be considered.

**Table 2. Goals of treatment from physician and patient side.**

<b>Goals of treatment (physician view)</b>	
Relief of symptoms	
Relief of coronary ischaemia	
Prevention of cardiac-related death	
Prevention of CAD progression and related conditions: myocardial infarction, left ventricular dysfunction, congestive heart failure	
<b>In physician terms</b>	<b>In patient terms</b>
Life prolongation (longevity influence)	Could it extend my life?
Improving quality of life	Will I feel more comfortable?
Premature cardiac death and MI prevention	Could it help me avoid heart attack or death? What will happen if I would do nothing?
Maintenance of independence	Will I be more physically active? Will I be able to maintain myself?
Relief of symptoms	Will I feel free from pain and shortness of breath?
Reduction the need for medical treatment	Could I take lesser pills?
Long term effect	How long will stay the effect of treatment?
<b>Treatment perspective</b>	
Hospital stay	How long will it take for me to feel better?
Inconvenience of procedure	Will I feel pain during and after procedure?
Risks of procedure: pain, cognitive impairment, stroke, CIN, bleeding, death	What bad could happen? Will it break my mind? Could I become disabled?
Possibility of recurrent procedure	Do I need repeat procedure?
Price (including medications/visits after procedure)	How much will it costs at all?
Use of DAPT in case of PCI	What should I do after procedure?

CAD: coronary artery disease; CIN: contrast-induced nephropathy; DAPT: dual antiplatelet therapy; MI: myocardial infarction; PCI: percutaneous coronary intervention.

The choice of a revascularization method should also be influenced by the social and psychological status of an elderly patient, and the way and how recovery will take place in the early and delayed postoperative period,<sup>[92]</sup> as well as the experience and results of given hospitals and operators performing the procedure.

## 6 If PCI, what way?

In contemporary practice, there are nearly 25% of PCI performed in patients  $\geq 75$  years and about 12% of PCI in patients  $\geq 80$  years, with good results.<sup>[93]</sup> And even the 90-year-old patients could reach an acceptable mortality and morbidity.<sup>[94]</sup>

When choosing PCI, physician needs to take into account the risks of bleeding, thrombosis, restenosis and other factors (Figure 2).

### 6.1 Approach

Radial approach should be encouraged as a primary in elderly as carrying a minimum of complications.<sup>[95]</sup> If technical difficulties and complications occurred during the procedure, it is possible to consider other options.

### 6.2 DES/BMS

DES effectively treat complex lesions and better prevent restenosis, i.e., reduce the rate of repeat procedures, but it raises the risk of bleeding after long DAPT and should not be used with low compliance and adherence to medical treatment, because of high risk of thrombosis in case of discontinuation.

New everolimus coated stents, which allow use of DAPT for six months without threat of thrombosis, could be an acceptable solution for elderly.<sup>[96]</sup> The XIMA trial compared DES *versus* BMS in octogenarians and demonstrated that the use of DES had not resulted in a higher percentage of bleeding and at the same time reduced MACE.<sup>[97]</sup> These results were confirmed in a large meta-analysis.<sup>[98]</sup>

### 6.3 Pharmacotherapy

One of the crucial things in PCI management in the elderly is choice of anticoagulation and antiplatelet medications and its dosage adjustment based on GFR. Contemporary evidence encourage the use of bivalirudin in the perioperative period, which is effective and safe.<sup>[99,100]</sup> In turn, ticagrelor should be avoided in elderly due to the increased risk of bleeding.<sup>[101]</sup>



#### 6.4 Staged/single

In relative healthy elderly with low operational risk, multiple single stenting can be safely performed.<sup>[102]</sup> In case of angiographic and clinical indications, including frailty, low GFR, high risk of bleeding, staged strategy may be used, when the second (and third, if necessary) intervention performed in 1–3 or 6 months after the first one according to the clinical condition.

### 7 If CABG, what way?

Despite the increasing proportions of elderly patients and worsening risk profile for elective CABG, mortality in elderly patients over recent decades has dramatically declined.<sup>[2]</sup> This is likely due to advancements and refinements of perioperative techniques and postoperative management (more left internal mammary artery and myocardial protection) and may be due to increased number of PCI performed in such patients.

There is evidence that minimally invasive cardiac surgery could improve survival in elderly patients undergoing CABG, in comparison with classic sternotomy.<sup>[103]</sup> The randomized Octopus trial on 281 low-risk patients had reported that the 1-year survival between CABG on-pump *versus* off-pump did not differ.<sup>[104]</sup> Similar results were obtained in the ROOBY trial.<sup>[105]</sup> Another trial has demonstrated that the off-pump surgery reduces the risk of stroke, atrial fibrillation, pneumonia and postoperative infections, and decreased hospital stay length.<sup>[106]</sup> There is also evidence that off-pump surgery in the elderly and high-risk patients reduces the incidence of stroke and time of intubation.<sup>[107,108]</sup>

### 8 Partial/complete revascularization

In the ARTS trial (including patients with diabetes) and BARI trial (excluding patients with diabetes) partial revascularization demonstrated no effect on long-term survival.<sup>[109]</sup>

The ARTS-II trial (with no elderly patients) reported that survival in patients with multivessel disease with partial revascularization did not differ among patients who received PCI and CABG. However, the rate of MACE (mostly due to repeat revascularization) was markedly higher in the PCI group; significantly lower survival was observed in the PCI patients with higher SYNTAX tertile.<sup>[110]</sup>

In a large analysis ( $n = 21,945$ ), patients with partial revascularization, who had undergone PCI, had a worse survival compared with complete revascularization. In patients older than 80 years, this trend, however, was not con-

firmed.<sup>[111]</sup> In contrast, Kim, *et al.*<sup>[112]</sup> reported that complete revascularization did not improve long-term survival both for DES and CABG patients with multi-vessel disease.

Complete revascularization should be considered in the elderly if it does not increase the invasiveness of the procedure. Physicians also need to take into account life expectancy, severity of symptoms, the presence of viable myocardium and other factors. To improve the quality of life and exertional capacity, partial revascularization is often enough.

### 9 Future trends

Hybrid revascularization—a combination of minimally invasive left internal thoracic artery grafting on the LAD and coronary stents implanted in other arteries during hospitalization—may be an ideal option for patients of older age groups. It allows reduced invasiveness of procedure and, therefore, short-term mortality, as well as achieving excellent long-term results.<sup>[113,114]</sup>

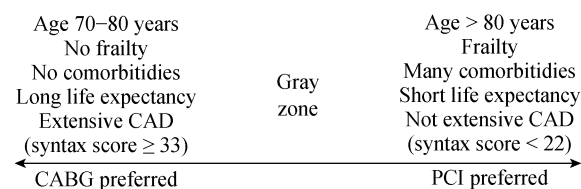
Bioabsorbable stents and stents coated with monoclonal antibodies probably effectively prevent restenosis and accelerate epithelization; stents on the guide with a very low-profile, special stents for bifurcation lesions, special devices for chronic occlusions may successfully treat more complex lesions in the elderly.<sup>[115]</sup>

Several trials have demonstrated the safety and efficiency of the intra-myocardial autologous cell engraftment,<sup>[116,117]</sup> but the technique is still the pilot phase.

### 10 Integrative approach

There is no doubt that CABG provides more effect on long-term survival and quality of life, and that PCI is less invasive. However, in the elderly only in some cases is the decision obvious (Figure 3).

Despite the fact that the European guidelines<sup>[77]</sup> recommend performing PCI in  $\geq 80$  years patients, one third of the elderly is frail, but two thirds are not,<sup>[70]</sup> so, the approaches should be different. Physicians or team of physicians face



**Figure 3. Extreme position of patient status in terms of selection between PCI and CABG in elderly.** CABG: coronary artery bypass surgery; CAD: coronary artery disease; PCI: percutaneous coronary intervention.

the task of evaluating a great number of factors in the complexity of their relationships (Figure 2). Most of all, some factors can be modified.

In fact, evaluating the necessity, possibility, all compounding factors, the selection of revascularization method and procedural features are performed as a single process simultaneously. Moreover, any factor can be an obstacle to performing the procedure, for example, the inability to control glucose blood level, excessive tortuosity of the vessels, the lack of money, or lack of patient desire to revascularize.

The main opposites, which need to be balanced when treating elderly patient: (1) early postoperative risk *versus* excellent long term results; and (2) more effective procedure which will reduce the recurrent medical visits *vs.* procedure which improve the quality of life.

Usually, there are no simple solutions. It is a kind of compromise, and in the case of frailty, or in patients with diabetes and end-stage renal disease, all options are not good.

## 11 Conclusions

There is a clear statement that age itself should not influence the selection of the method of treatment. In the lack of evidence, we should take into account plenty of factors, the most important of which is frailty. Decisions should be based on comprehensive risk/benefit profile made by physicians from different point of view. Optimal medical therapy, including control of risk factors and pharmacological agents, is still a corner stone. Large randomized trials in older patients with stable angina are strongly warranted to obtain reliable data to help in the management of this high-risk patient group.

## References

- Singh M, Peterson ED, Roe MT, *et al.* Trends in the association between age and in-hospital mortality after percutaneous coronary intervention: National Cardiovascular Data Registry experience. *Circ Cardiovasc Interv* 2009; 2: 20–26.
- Yanagawa B, Algarni KD, Yau TM, *et al.* Improving results for coronary artery bypass graft surgery in the elderly. *Eur J Cardiothorac Surg* 2012; 42: 507–512.
- Pfisterer M. Long-term outcome in elderly patients with chronic angina managed invasively versus by optimized medical therapy: four-year follow-up of the randomized Trial of Invasive versus Medical therapy in Elderly patients (TIME). *Circulation* 2004; 110: 1213–1218.
- Graham MM. Survival After Coronary Revascularization in the Elderly. *Circulation* 2002; 105: 2378–2384.
- Trial of invasive versus medical therapy in elderly patients with chronic symptomatic coronary-artery disease (TIME): a randomised trial. *Lancet* 2001; 358: 951–957.
- Ramanathan KB, Weiman DS, Sacks J, *et al.* Percutaneous intervention versus coronary bypass surgery for patients older than 70 years of age with high-risk unstable angina. *Ann Thorac Surg* 2005; 80: 1340–1346.
- Mullany CJ, Mock MB, Brooks MM, *et al.* Effect of age in the Bypass Angioplasty Revascularization Investigation (BARI) randomized trial. *Ann Thorac Surg* 1999; 67: 396–403.
- Mercado N, Wijns W, Serruys PW, *et al.* One-year outcomes of coronary artery bypass graft surgery versus percutaneous coronary intervention with multiple stenting for multisystem disease: a meta-analysis of individual patient data from randomized clinical trials. *J Thorac Cardiovasc Surg* 2005; 130: 512–519.
- Rodriguez AE, Baldi J, Fernández Pereira C, *et al.* Five-year follow-up of the argentine randomized trial of coronary angioplasty with stenting versus coronary bypass surgery in patients with multiple vessel disease (ERACI II). *J Am Coll Cardiol* 2005; 46: 582–588.
- Serruys PW, Ong ATL, van Herwerden LA, *et al.* Five-year outcomes after coronary stenting versus bypass surgery for the treatment of multivessel disease: the final analysis of the Arterial Revascularization Therapies Study (ARTS) randomized trial. *J Am Coll Cardiol* 2005; 46: 575–581.
- The final 10-year follow-up results from the BARI randomized trial. *J Am Coll Cardiol* 2007; 49: 1600–1606.
- Hueb W, Lopes N, Gersh BJ, *et al.* Ten-year follow-up survival of the Medicine, Angioplasty, or Surgery Study (MASS II): a randomized controlled clinical trial of 3 therapeutic strategies for multivessel coronary artery disease. *Circulation* 2010; 122: 949–957.
- Booth J, Clayton T, Pepper J, *et al.* Randomized, controlled trial of coronary artery bypass surgery versus percutaneous coronary intervention in patients with multivessel coronary artery disease: six-year follow-up from the Stent or Surgery Trial (SoS). *Circulation* 2008; 118: 381–388.
- Daemen J, Boersma E, Flather M, *et al.* Long-term safety and efficacy of percutaneous coronary intervention with stenting and coronary artery bypass surgery for multivessel coronary artery disease: a meta-analysis with 5-year patient-level data from the ARTS, ERACI-II, MASS-II, and SoS trials. *Circulation* 2008; 118: 1146–1154.
- Bravata DM, Gienger AL, McDonald KM, *et al.* Systematic review: the comparative effectiveness of percutaneous coronary interventions and coronary artery bypass graft surgery. *Ann Intern Med* 2007; 147: 703–716.
- Hlatky MA, Boothroyd DB, Bravata DM, *et al.* Coronary artery bypass surgery compared with percutaneous coronary interventions for multivessel disease: a collaborative analysis of individual patient data from ten randomised trials. *Lancet* 2009; 373: 1190–1197.
- Loop FD, Lytle BW, Cosgrove DM, *et al.* Influence of the internal-mammary-artery graft on 10-year survival and other cardiac events. *N Engl J Med* 1986; 314: 1–6.

- 18 Kappetein AP, Dawkins KD, Mohr FW, *et al.* Current percutaneous coronary intervention and coronary artery bypass grafting practices for three-vessel and left main coronary artery disease. Insights from the SYNTAX run-in phase. *Eur J Cardiothorac Surg* 2006; 29: 486–491.
- 19 Mohr FW, Morice MC, Kappetein AP, *et al.* Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. *Lancet* 2013; 381: 629–638.
- 20 Malenka DJ, Leavitt BJ, Hearne MJ, *et al.* Comparing long-term survival of patients with multivessel coronary disease after CABG or PCI: analysis of BARI-like patients in northern New England. *Circulation* 2005; 112: I371–I376.
- 21 Peterson ED, Alexander KP, Malenka DJ, *et al.* Multicenter experience in revascularization of very elderly patients. *Am Heart J* 2004; 148: 486–492.
- 22 McKellar SH, Brown ML, Frye RL, *et al.* Comparison of coronary revascularization procedures in octogenarians: a systematic review and meta-analysis. *Nat Clin Pract Cardiovasc Med* 2008; 5: 738–746.
- 23 Weintraub WS, Grau-Sepulveda MV, Weiss JM, *et al.* Comparative effectiveness of revascularization strategies. *N Engl J Med* 2012; 366: 1467–1476.
- 24 Kurlansky P, Herbert M, Prince S, *et al.* Coronary artery revascularization evaluation--a multicenter registry with seven years of follow-up. *J Am Heart Assoc* 2013; 2: e000162.
- 25 Hannan EL, Zhong Y, Berger PB, *et al.* Comparison of intermediate-term outcomes of coronary artery bypass grafting versus drug-eluting stents for patients  $\geq 75$  years of age. *Am J Cardiol* 2014; 113: 803–808.
- 26 Batchelor WB, Anstrom KJ, Muhlbaier LH, *et al.* Contemporary outcome trends in the elderly undergoing percutaneous coronary interventions: results in 7,472 octogenarians. National Cardiovascular Network Collaboration. *J Am Coll Cardiol* 2000; 36: 723–730.
- 27 Newman AB, Naydeck BL, Sutton-Tyrrell K, *et al.* Coronary Artery Calcification in Older Adults to Age 99: Prevalence and Risk Factors. *Circulation* 2001; 104: 2679–2684.
- 28 De Felice F, Fiorilli R, Parma A, *et al.* Clinical outcome of patients with chronic total occlusion treated with drug-eluting stents. *Int J Cardiol* 2009; 132: 337–341.
- 29 Alam M, Virani SS, Shahzad SA, *et al.* Comparison by meta-analysis of percutaneous coronary intervention versus coronary artery bypass grafting in patients with a mean age of  $\geq 70$  years. *Am J Cardiol* 2013; 112: 615–622.
- 30 Serruys PW, Morice MC, Kappetein AP, *et al.* Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med* 2009; 360: 961.
- 31 Hakeem A, Garg N, Bhatti S, *et al.* Effectiveness of percutaneous coronary intervention with drug-eluting stents compared with bypass surgery in diabetics with multivessel coronary disease: comprehensive systematic review and meta-analysis of randomized clinical data. *J Am Heart Assoc* 2013; 2: e000354.
- 32 Verma S, Farkouh ME, Yanagawa B, *et al.* Comparison of coronary artery bypass surgery and percutaneous coronary intervention in patients with diabetes: a meta-analysis of randomised controlled trials. *Lancet Diabetes Endocrinol* 2013; 1: 317–328.
- 33 Chirumamilla AP, Wilson MF, Wilding GE, *et al.* Outcome of renal insufficiency patients undergoing coronary artery bypass graft surgery. *Cardiology* 2008; 111: 23–29.
- 34 Russ M, Werdan K, Cremer J, *et al.* Different treatment options in chronic coronary artery disease: when is it the time for medical treatment, percutaneous coronary intervention or aortocoronary bypass surgery? *Dtsch Arztebl Int* 2009; 106: 253–261.
- 35 Best PJM, Lennon R, Ting HH, *et al.* The impact of renal insufficiency on clinical outcomes in patients undergoing percutaneous coronary interventions. *J Am Coll Cardiol* 2002; 39: 1113–1119.
- 36 Cooper WA, O'Brien SM, Thourani VH, *et al.* Impact of renal dysfunction on outcomes of coronary artery bypass surgery: results from the Society of Thoracic Surgeons National Adult Cardiac Database. *Circulation* 2006; 113: 1063–1070.
- 37 Hemmelgarn BR, Southern D, Culleton BF, *et al.* Survival after coronary revascularization among patients with kidney disease. *Circulation* 2004; 110: 1890–1895.
- 38 Reddan DN, Szczech LA, Tuttle RH, *et al.* Chronic kidney disease, mortality, and treatment strategies among patients with clinically significant coronary artery disease. *J Am Soc Nephrol* 2003; 2373–2380.
- 39 Ashrith G, Lee VV, Elayda MA, *et al.* Short- and long-term outcomes of coronary artery bypass grafting or drug-eluting stent implantation for multivessel coronary artery disease in patients with chronic kidney disease. *Am J Cardiol* 2010; 106: 348–353.
- 40 Wang ZI, Zhou YJ, Liu YY, *et al.* Comparison of drug-eluting stents and coronary artery bypass grafting for the treatment of multivessel coronary artery disease in patients with chronic kidney disease. *Circ J* 2009; 73: 1228–1234.
- 41 Chang TI, Leong TK, Kazi DS, *et al.* Comparative effectiveness of coronary artery bypass grafting and percutaneous coronary intervention for multivessel coronary disease in a community-based population with chronic kidney disease. *Am Heart J* 2013; 165: 800–808.
- 42 Wilson MF, Baig MK, Ashraf H. Quality of life in octogenarians after coronary artery bypass grafting. *Am J Cardiol* 2005; 95: 761–764.
- 43 Dacey LJ, Likosky DS, Ryan TJ, *et al.* Long-term survival after surgery versus percutaneous intervention in octogenarians with multivessel coronary disease. *Ann Thorac Surg* 2007; 84: 1904–1911.
- 44 Kaiser C, Kuster GM, Erne P, *et al.* Risks and benefits of optimised medical and revascularisation therapy in elderly patients with angina--on-treatment analysis of the TIME trial.

- Eur Heart J* 2004; 25: 1036–1042.
- 45 Graham MM, Norris CM, Galbraith PD, *et al.* Quality of life after coronary revascularization in the elderly. *Eur Heart J* 2006; 27: 1690–1698.
  - 46 Kamiya M, Takayama M, Takano H, *et al.* Clinical outcome and quality of life of octogenarian patients following percutaneous coronary intervention or surgical coronary revascularization. *Circ J* 2007; 71: 847–854.
  - 47 Baig K, Harling L, Papanikitas J, *et al.* Does coronary artery bypass grafting improve quality of life in elderly patients? *Interact Cardiovasc Thorac Surg* 2013; 17: 542–553.
  - 48 Shan L, Saxena A, McMahon R, *et al.* Coronary artery bypass graft surgery in the elderly: a review of postoperative quality of life. *Circulation* 2013; 128: 2333–2343.
  - 49 Cohen DJ, Van Hout B, Serruys PW, *et al.* Quality of life after PCI with drug-eluting stents or coronary-artery bypass surgery. *N Engl J Med* 2011; 364: 1016–1026.
  - 50 Borkon AM, Muehlebach GF, House J, *et al.* A comparison of the recovery of health status after percutaneous coronary intervention and coronary artery bypass. *Ann Thorac Surg* 2002; 74: 1526–1530.
  - 51 Szygula-Jurkiewicz B, Zembala M, Wilczek K, *et al.* Health related quality of life after percutaneous coronary intervention versus coronary artery bypass graft surgery in patients with acute coronary syndromes without ST-segment elevation. 12-month follow up. *Eur J Cardiothorac Surg* 2005; 27: 882–886.
  - 52 Hoffman SN, TenBrook JA, Wolf MP, *et al.* A meta-analysis of randomized controlled trials comparing coronary artery bypass graft with percutaneous transluminal coronary angioplasty: one- to eight-year outcomes. *J Am Coll Cardiol* 2003; 41: 1293–1304.
  - 53 Funder KS, Steinmetz J, Rasmussen LS. Cognitive dysfunction after cardiovascular surgery. *Minerva Anesthesiol* 2009; 75: 329–332.
  - 54 Rudolph JL, Schreiber KA, Culley DJ, *et al.* Measurement of post-operative cognitive dysfunction after cardiac surgery: a systematic review. *Acta Anaesthesiol Scand* 2010; 54: 663–677.
  - 55 Währborg P, Booth JE, Clayton T, *et al.* Neuropsychological outcome after percutaneous coronary intervention or coronary artery bypass grafting: results from the Stent or Surgery (SoS) Trial. *Circulation* 2004; 110: 3411–3417.
  - 56 Rosengart TK, Sweet J, Finnin EB, *et al.* Neurocognitive functioning in patients undergoing coronary artery bypass graft surgery or percutaneous coronary intervention: evidence of impairment before intervention compared with normal controls. *Ann Thorac Surg* 2005; 80: 1327–1334.
  - 57 Selnes OA, Grega MA, Bailey MM, *et al.* Do management strategies for coronary artery disease influence 6-year cognitive outcomes? *Ann Thorac Surg* 2009; 88: 445–454.
  - 58 Stroobant N, Vingerhoets G. Pre-existing cognitive impairment in candidates for cardiac surgery: an overview. *Heart* 2009; 95: 1820–1825.
  - 59 Bruce KM, Yelland GW, Smith JA, *et al.* Recovery of cognitive function after coronary artery bypass graft operations. *Ann Thorac Surg* 2013; 95: 1306–1313.
  - 60 Selnes OA. Invited commentary. *Ann Thorac Surg* 2013; 95: 1313–1314.
  - 61 Mutch WAC, Fransoo RR, Campbell BI, *et al.* Dementia and depression with ischemic heart disease: a population-based longitudinal study comparing interventional approaches to medical management. *PLoS One* 2011; 6: e17457.
  - 62 Hlatky MA, Boothroyd DB, Baker L, *et al.* Comparative effectiveness of multivessel coronary bypass surgery and multivessel percutaneous coronary intervention: a cohort study. *Ann Intern Med* 2013; 158: 727–734.
  - 63 From AM, Badarin FJ Al, Cha SS, *et al.* PCI with drug-eluting stents versus coronary artery bypass surgery for multivessel coronary artery disease: a meta-analysis of data from the ARTS II, CARDia, ERACI III, and SYNTAX studies and systematic review of observational data. *Eurointervention* 2010; : 269–276.
  - 64 Palmerini T, Biondi-Zoccai G, Reggiani LB, *et al.* Risk of stroke with coronary artery bypass graft surgery compared with percutaneous coronary intervention. *J Am Coll Cardiol* 2012; 60: 798–805.
  - 65 Peterson ED, Alexander KP, Malenka DJ, *et al.* Multicenter experience in revascularization of very elderly patients. *Am Heart J* 2004; 148: 486–492.
  - 66 Tarakji KG, Sabik JF, Bhudia SK, *et al.* Temporal onset, risk factors, and outcomes associated with stroke after coronary artery bypass grafting. *JAMA* 2011; 305: 381–390.
  - 67 Marui A, Kimura T, Tanaka S, *et al.* Comparison of frequency of postoperative stroke in off-pump coronary artery bypass grafting versus on-pump coronary artery bypass grafting versus percutaneous coronary intervention. *Am J Cardiol* 2012; 110: 1773–1778.
  - 68 Crosby G, Culley DJ, Hyman BT. Preoperative cognitive assessment of the elderly surgical patient: a call for action. *Anesthesiology* 2011; 114: 1265–1268.
  - 69 Clegg A, Young J, Iliffe S, *et al.* Frailty in elderly people. *Lancet* 2013; 381: 752–762.
  - 70 Iqbal J, Denvir M, Gunn J. Frailty assessment in elderly people. *Lancet* 2013; 381: 1985–1986.
  - 71 Gharacholou SM, Roger VL, Lennon RJ, *et al.* Comparison of frail patients versus nonfrail patients  $\geq 65$  years of age undergoing percutaneous coronary intervention. *Am J Cardiol* 2012; 109: 1569–1575.
  - 72 Singh M, Rihal CS, Lennon RJ, *et al.* Influence of frailty and health status on outcomes in patients with coronary disease undergoing percutaneous revascularization. *Circ Cardiovasc Qual Outcomes* 2011; 4: 496–502.
  - 73 Robinson TN, Wu DS, Pointer L, *et al.* Simple frailty score predicts postoperative complications across surgical specialties. *Am J Surg* 2013; 206: 544–550.
  - 74 Sündermann SH, Dademasch A, Seifert B, *et al.* Frailty is a predictor of short- and mid-term mortality after elective

- cardiac surgery independently of age. *Interact Cardiovasc Thorac Surg* 2014; 18: 580–585.
- 75 Chaudhry SI, Gill TM. Geriatric assessment to improve risk stratification in older patients undergoing coronary revascularization. *Circ Cardiovasc Qual Outcomes* 2011; 4: 491–492.
  - 76 Partridge JSL, Harari D, Dhesei JK. Frailty in the older surgical patient: a review. *Age Ageing* 2012; 41: 142–147.
  - 77 Montalescot G, Sechtem U, Achenbach S, et al. 2013 ESC guidelines on the management of stable coronary artery disease: The Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J* 2013; 34: 2949–3003.
  - 78 Makary MA, Segev DL, Pronovost PJ, et al. Frailty as a predictor of surgical outcomes in older patients. *J Am Coll Surg* 2010; 210: 901–908.
  - 79 Coylewright M, Shepel K, Leblanc A, et al. Shared decision making in patients with stable coronary artery disease: PCI choice. *PLoS One* 2012; 7: e49827.
  - 80 Chandrasekharan DP, Taggart DP. Informed consent for interventions in stable coronary artery disease: problems, etiologies, and solutions. *Eur J Cardiothorac Surg* 2011; 39: 912–917.
  - 81 Hannan EL, Cozzens K, Samadashvili Z, et al. Appropriateness of coronary revascularization for patients without acute coronary syndromes. *J Am Coll Cardiol* 2012; 59: 1870–1876.
  - 82 Bradley SM, Chan PS, Spertus JA, et al. Hospital percutaneous coronary intervention appropriateness and in-hospital procedural outcomes: insights from the NCDR. *Circ Cardiovasc Qual Outcomes* 2012; 5: 290–297.
  - 83 Lin GA, Dudley RA, Redberg RF. Cardiologists' use of percutaneous coronary interventions for stable coronary artery disease. *Arch Intern Med* 2007; 167: 1604–1609.
  - 84 Schwartz L. Therapeutic options in coronary artery disease: focusing on the guidelines. *Can J Cardiol* 2009; 25: 19–24.
  - 85 Gibbons RJ. Get with the guidelines: a new chapter? *Circulation* 2010; 121: 194–196.
  - 86 Baker BYJ. Multi-vessel heart disease: The 'best' treatment may not be what you think. *DukeMed Mag* 2008; 8: 48–51.
  - 87 Singh M, Alexander K, Roger VL, et al. Frailty and its potential relevance to cardiovascular care. *Mayo Clin Proc* 2008; 83: 1146–1153.
  - 88 Fried TR, Van Ness PH, Byers AL, et al. Changes in preferences for life-sustaining treatment among older persons with advanced illness. *J Gen Intern Med* 2007; 22: 495–501.
  - 89 Fried TR, Bradley EH, Towle VR, et al. Understanding the treatment preferences of seriously ill patients. *N Engl J Med* 2002; 346: 1061–1066.
  - 90 Thomson P, Niven CA, Peck DF, et al. Patients' and partners' health-related quality of life before and 4 months after coronary artery bypass grafting surgery. *BMC Nurs* 2013; 12: 16.
  - 91 Tully PJ, Baker RA. Depression, anxiety, and cardiac morbidity outcomes after coronary artery bypass surgery: a contemporary and practical review. *J Geriatr Cardiol* 2012; 9: 197–208.
  - 92 Natarajan A, Samadian S, Clark S. Coronary artery bypass surgery in elderly people. *Postgrad Med J* 2007; 83: 154–158.
  - 93 Bauer T, Möllmann H, Weidinger F, et al. Predictors of hospital mortality in the elderly undergoing percutaneous coronary intervention for acute coronary syndromes and stable angina. *Int J Cardiol* 2011; 151: 164–169.
  - 94 Biondi Zoccai G, Abbate A, D'Ascenzo F, et al. Percutaneous coronary intervention in nonagenarians: pros and cons. *J Geriatr Cardiol* 2013; 10: 82–90.
  - 95 Secco GG, Marinucci L, Uguccioni L, et al. Transradial versus transfemoral approach for primary percutaneous coronary interventions in elderly patients. *J Invasive Cardiol* 2013; 25: 254–256.
  - 96 Kedhi E, Stone GW, Kereiakes DJ, et al. Stent thrombosis: insights on outcomes, predictors and impact of dual antiplatelet therapy interruption from the SPIRIT II, SPIRIT III, SPIRIT IV and COMPARE trials. *EuroIntervention* 2012; 8: 599–606.
  - 97 de Belder A, de la Torre Hernandez JM, Lopez-Palop R, et al. A prospective randomized trial of everolimus-eluting stents versus bare-metal stents in octogenarians: the XIMA Trial (Xience or Vision Stents for the Management of Angina in the Elderly). *J Am Coll Cardiol* 2014; 63: 1371–1375.
  - 98 Gao L, Hu X, Liu YQ, et al. Comparison of coronary DES and BMS in octogenarians: A systematic review and meta-analysis. *J Geriatr Cardiol* 2013; 10: 336–343.
  - 99 Marso SP, Amin AP, House JA, et al. Association between use of bleeding avoidance strategies and risk of periprocedural bleeding among patients undergoing percutaneous coronary intervention. *JAMA* 2010; 303: 2156–2164.
  - 100 Chhatrivala AK, Amin AP, Kennedy KF, et al. Association between bleeding events and in-hospital mortality after percutaneous coronary intervention. *JAMA* 2013; 309: 1022–1029.
  - 101 Cannon CP, Harrington RA, James S, et al. Comparison of ticagrelor with clopidogrel in patients with a planned invasive strategy for acute coronary syndromes (PLATO): a randomised double-blind study. *Lancet* 2010; 375: 283–293.
  - 102 Hannan EL, Samadashvili Z, Walford G, et al. Staged versus one-time complete revascularization with percutaneous coronary intervention for multivessel coronary artery disease patients without ST-elevation myocardial infarction. *Circ Cardiovasc Interv* 2013; 6: 12–20.
  - 103 Barsoum EA, Azab B, Shah N, et al. Long-term mortality in minimally invasive compared with sternotomy coronary artery bypass surgery in the geriatric population (75 years and older patients). *Eur J Cardiothorac Surg* 2015; 47: 862–867.
  - 104 Nathoe HM, van Dijk D, Jansen EWL, et al. A comparison of on-pump and off-pump coronary bypass surgery in low-risk patients. *N Engl J Med* 2003; 348: 394–402.
  - 105 Shroyer AL, Grover FL, Hattler B, et al. On-pump versus

- off-pump coronary-artery bypass surgery. *N Engl J Med* 2009; 361: 1827–1837.
- 106 Sedrakyan A, Wu AW, Parashar A, *et al.* Off-pump surgery is associated with reduced occurrence of stroke and other morbidity as compared with traditional coronary artery bypass grafting: a meta-analysis of systematically reviewed trials. *Stroke* 2006; 37: 2759–2769.
- 107 Al-Ruzzeh S, Nakamura K, Athanasiou T, *et al.* Does off-pump coronary artery bypass (OPCAB) surgery improve the outcome in high-risk patients?: a comparative study of 1398 high-risk patients. *Eur J Cardiothorac Surg* 2003; 23: 50–55.
- 108 Nagpal a D, Bhatnagar G, Cutrara CA, *et al.* Early outcomes of coronary artery bypass with and without cardiopulmonary bypass in octogenarians. *Can J Cardiol* 2006; 22: 849–853.
- 109 Teirstein PS. The dueling hazards of incomplete revascularization and incomplete data. *Circulation* 2006; 113: 2380–2382.
- 110 Sarno G, Garg S, Onuma Y, *et al.* Impact of completeness of revascularization on the five-year outcome in percutaneous coronary intervention and coronary artery bypass graft patients (from the ARTS-II study). *Am J Cardiol* 2010; 106: 1369–1375.
- 111 Hannan EL, Racz M, Holmes DR, *et al.* Impact of completeness of percutaneous coronary intervention revascularization on long-term outcomes in the stent era. *Circulation* 2006; 113: 2406–2412.
- 112 Kim YH, Park DW, Lee JY, *et al.* Impact of angiographic complete revascularization after drug-eluting stent implantation or coronary artery bypass graft surgery for multivessel coronary artery disease. *Circulation* 2011; 123: 2373–2381.
- 113 Harskamp RE, Puskas JD, Tijssen JG, *et al.* Comparison of hybrid coronary revascularization versus coronary artery bypass grafting in patients  $\geq$  65 years with multivessel coronary artery disease. *Am J Cardiol* 2014; 114: 224–229.
- 114 Jones ML, Qiu S, Sudarshan C. Perioperative outcomes in hybrid versus conventional surgical coronary artery revascularisation. *Interact Cardiovasc Thorac Surg* 2010; 11: 292–296.
- 115 Ma X, Wu T, Robich MP, *et al.* Drug-eluting stents not associated with worse long-term outcome than bare-metal stents. *Nat Clin Pract Cardiovasc Med* 2007; 4: 348–348.
- 116 Cheng K, Wu F, Cao F. Intramyocardial autologous cell engraftment in patients with ischaemic heart failure: a meta-analysis of randomised controlled trials. *Heart Lung Circ* 2013; 22: 887–894.
- 117 Van Ramshorst J, Beeres SLMA, Rodrigo SF, *et al.* Effect of intramyocardial bone marrow-derived mononuclear cell injection on cardiac sympathetic innervation in patients with chronic myocardial ischemia. *Int J Cardiovasc Imaging* 2014; 30: 583–589.