



Percutaneous coronary intervention in nonagenarians: pros and cons

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Abstract

Percutaneous coronary intervention is a mainstay in the management of symptomatic or high-risk coronary artery disease. The bulk of clinical evidence and experience underlying this fact relies, however, on relatively young patients. Indeed, few data of very limited quality are available which adequately define the risk-benefit and cost-benefit profile of coronary angioplasty and stenting in very old subjects, such as those of 90 years of age or older (i.e., nonagenarians). The aim of this review is to provide a concise, yet practical, synthesis of the available evidence on percutaneous coronary revascularization in the very elderly. The main arguments elaborated upon are to what extent we can extrapolate findings from studies including younger patients to nonagenarians, whether we should provide higher priority to prognosis or quality of life in such patients, and whether we can afford to allocate vast resources to care for such subjects in an era of financial constraints. Our review of 18 studies and 1082 patients suggest that percutaneous coronary intervention is feasible and associated with acceptable short- and long-term results in this population, which is nonetheless fraught with a high mortality risk irrespective of the revascularization procedure. Accordingly, the pros and cons of percutaneous coronary intervention should be carefully weighed when considering this treatment in nonagenarians.

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1 Introduction

Thanks to widespread improvements in the delivery of preventive, diagnostic and treatment strategies, the elderly and the very elderly (≥ 85 –90 years) are becoming an ever larger subset of the population.^[1–3] Despite such prolonged life expectancy, both common and uncommon conditions tend to cluster in these patients, such that they often and concomitantly have several risk factors, co-morbidities, and unfavorable diatheses.^[4,5] Moreover, octogenarians and, even more so in nonagenarians, also often have unfavorable prognostic features which are incompletely captured by standard diagnostic and prognostic tools, but that can very

ominously impact on quality of life, symptoms, and survival. The latter cluster is often called frailty.^[6–9]

Coronary artery disease is highly prevalent and symptomatic in the elderly,^[10] who often show multivessel disease and complex lesion anatomy.^[11,12] Moreover, they are at increased risk of type 2 myocardial infarction (i.e., infarction secondary to ischemia due to an imbalance between oxygen demand and supply, for example, coronary spasms, anemia, or hypotension) and stress induced cardiomyopathy, which may represent a diagnostic and management challenge, especially given the presence of several co-morbidities. Age is also a very common risk predictor for both early and long-term adverse events in patients with coronary artery disease, irrespective of their conservative or invasive management.^[13,14] Whenever coronary artery disease portends an unfavorable short-term prognosis, or is symptomatic despite medical therapy, percutaneous or surgical revascularization, theoretically, can be envisioned irrespective of the patient's age.^[15] Despite the apparent safety of coronary artery bypass surgery in selected nonagenarians, this treatment choice remains very

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uncommon.^[16] Conversely, percutaneous coronary intervention represents an ideal revascularization approach in these subjects, given its minimal invasiveness and suitability for staging.^[17] This bias against surgery for coronary revascularization in the very elderly with coronary artery disease is similar to the one against surgical valve replacement in such subjects when they also have aortic valve stenosis, which is a relatively common combination. Indeed, transcatheter aortic valve replacement shares with percutaneous coronary intervention several favorable features, mainly due to its lower invasiveness.

Percutaneous coronary intervention is not, however, a panacea. Early and long-term adverse events are not uncommon in those undergoing implantation of coronary stents, which are routinely implanted in the vast majority of patients.^[18,19] Moreover, stenting itself requires potent peri-procedural antithrombotic therapy,^[15,20–23] and a commitment to ≥ 1 –6 months of dual antiplatelet therapy, depending on stent type and admission diagnosis.^[15,24,25] Indeed, after having appraised coronary anatomy, the decision to proceed or not with coronary revascularization relies on the complex and comprehensive weighing of the likelihood of procedural success, ischemic/thrombotic risk, and bleeding risk.^[26–28] This is even truer in the very elderly, such as those ≥ 90 years of age. Unfortunately, most randomized clinical trials fail to screen or enroll very old patients, and thus cannot directly guide clinical decision making.^[29,30] Conversely, some observational studies on this topic have been reported, with apparently conflicting results.^[3,31,32] We thus aimed to provide a comprehensive and updated perspective on the outlook of percutaneous coronary intervention in nonagenarians, directed at the practicing physician as well as the clinical researcher wishing to more poignantly face this clinical conundrum.

2 Reviewing approach

This work was not designed as a systematic review, as this was beyond our scope and would have limited our room for the inclusion of additional elements outside of the realm of shortlisted studies. Nonetheless, a systematic search of the literature according to Biondi-Zoccai *et al.*^[33] was performed in MEDLINE/PubMed exploiting the following string: nonagenarian* and (PCI or PTCA or Angioplasty or Stent*) and coronary. Shortlisted studies, as well as suitable reviews and book chapters including references, were analyzed in detail (exploiting backward snowballing, *i.e.*, the systematic analysis of studies quoted in the originally short-listed work).

3 Percutaneous coronary intervention in the current era

Percutaneous coronary intervention can today be undertaken with very favorable early and long-term results as long as a number of technical and strategic choices are correctly made. This holds even truer in nonagenarians. First, radial or ulnar arteries should be the default access sites to minimize bleeding and ensuing adverse events.^[27,34,35] Second, coronary angiography should be performed with high-quality imaging systems,^[36,37] possibly complemented by stent boost or similar imaging approaches. While fractional flow reserve, intravascular ultrasound, or optical coherence tomography can also be envisioned in selected cases, their potential to increase the rate of peri-procedural complications should not be overlooked.^[38–45] In addition, care should be taken to minimize the risk of contrast-associated nephropathy, *e.g.*, by limiting contrast load and optimizing fluid status avoiding dehydration or volume overload, as well as using dedicated drugs and devices.^[46–48]

Once a decision is made to proceed with coronary stenting, a culprit-only revascularization approach should be envisioned in all cases of multivessel disease but the exceptional ones.^[17,49–51] Accordingly, lesion preparation and post-stenting optimization should be parsimoniously pursued, as these may indeed have a detrimental impact on peri-procedural events.^[52] Coronary bifurcations should be approached with a conservative stance, unless a large side branch does compromise itself causing symptoms or instability.^[53,54] Thus, a provisional stenting strategy should be pursued in most coronary bifurcation lesions.^[18,55] Moreover, diffuse (*e.g.*, full metal jacket) stenting should be avoided and spot stenting adopted instead, to minimize the risk of stent thrombosis.^[56,57]

Stent choice should be based on a comprehensive assessment of the risk of restenosis, thrombosis, bleeding, and non-compliance.^[58–60] Bare-metal stents can be considered the device of first choice in nonagenarians, given the prevailing goal of minimizing the risk of bleeding.^[61] However, recent data suggest that everolimus-eluting stents require dual antiplatelet therapy for six months or less,^[62] and are associated with fewer stent thromboses than bare-metal stents.^[63,64] Accordingly, such new-generation devices might be envisioned in selected nonagenarians, especially in the future when further reductions in the price of stents are expected. Indeed, several studies reporting on percutaneous coronary intervention in nonagenarians already reported rather high rates of drug-eluting stent usage (up to 100%).^[65] Whether this was an appropriate choice in the cited individual cases is open to debate.

Finally, it is paramount to tailor antithrombotic therapy before, during, and after percutaneous coronary intervention in nonagenarians. Low-dose unfractionated heparin or, even better, bivalirudin should be the anticoagulant used during the procedure.^[65,66] Aspirin should be prescribed well before revascularization and thereafter lifelong, at low (≤ 100 mg/d) doses.^[59,67,68] Clopidogrel should be the purinergic receptor P2Y₁₂, G-protein coupled, 12 (P2Y₁₂) blocker of choice, given its ease of use, friendly therapeutic window, and low cost.^[69,70] Ticagrelor might still be envisioned in very selected nonagenarians,^[69] whereas prasugrel might be avoided in most patients given its established risk of bleeding.^[23,70] It is unclear whether platelet function testing is beneficial in general, and even more so in nonagenarians.^[71–73]

4 Pros of percutaneous coronary intervention in nonagenarians

Percutaneous coronary intervention offers several potential advantages in the very elderly. First, its low invasiveness and limited likelihood for cognitive impairment (at odds with coronary artery bypass surgery) make it appealing for physicians, patients, and relatives.^[74] Moreover, coronary stenting can be staged if multivessel disease is present and repeated if deemed necessary when symptoms recur. Indeed, repeat procedures are not now necessarily considered a failure of coronary stenting, but rather an inherent characteristic of this revascularization strategy.^[75] In addition, percutaneous coronary intervention may provide greater symptomatic relief than medical therapy, especially if clinically relevant stenoses are unequivocally identified.^[38,39,76–78]

Percutaneous coronary intervention represents a very appealing option especially for patients with ST-elevation myocardial infarction. In such subjects, an early price of increased complication rates with an invasive approach can be expected. However, if the patient is reasonably fit and expected to live an autonomous life style after discharge, percutaneous coronary intervention is the best means to achieve myocardial salvage and secure vessel patency.^[79] Even in patients with non-ST-elevation myocardial infarction, percutaneous coronary intervention can provide meaningful clinical benefits, especially if the patient is symptomatic despite maximal medical therapy or shows clinical instability.^[10] Care should be taken, however, to refrain from complex and anatomically complete revascularization attempts, which are likely going to be fraught with an increased risk of fatal and non-fatal complications.^[49,80] Conversely, percutaneous coronary inter-

vention should be reserved to few nonagenarian subjects with stable coronary artery disease, as medical therapy alone can provide adequate relief of symptoms and reduce the risk of adverse events in the vast majority of them.^[81,82]

5 Cons of percutaneous coronary intervention in nonagenarians

Despite the favorable features above, percutaneous coronary intervention is not an inherently good approach in nonagenarians, who are by definition very frail and at high risk of recurrences and adverse events, irrespective of their admission diagnosis and coronary anatomy. First, coronary stenting is an invasive act, possibly associated with local access site complications, such as bleeding, dissection, perforation or thrombosis. Despite the reduction in the risk of these events by systematically adopting radial access, access complications may still occur occasionally.^[83,84]

Coronary instrumentation is also a possible harbinger of complications, mainly coronary thrombosis, dissection or perforation.^[85,86] Moreover, the higher prevalence of diffuse disease, severe calcification, and tortuosity in nonagenarians makes this patient group at higher risk of such complications as well as technical or procedural failure (e.g., in case of suboptimal stent expansion). Whereas intravascular ultrasound and optical coherence tomography might be handy to reduce the risk of these complications, they also may lead to additional complications and generally cause an overuse of devices and prolong the procedure.^[45,87]

Even after the procedure is completed, apparently in an uneventful fashion, adverse events may occur. Indeed, age is a potent and independent predictor of death, myocardial infarction, repeat revascularization, stent thrombosis, and repeat hospitalization after percutaneous coronary intervention.^[13,57] Accordingly, careful follow-up should be envisioned and medical therapy should be maximized in dosages and include aspirin, an angiotensin-converting enzyme inhibitor, a beta-adrenergic receptor blocker, a P2Y₁₂ blocker, and a statin whenever possible and not contraindicated. Utmost care should be taken to maximize compliance and adherence to treatment, especially for dual antiplatelet therapy, as discontinuation of either aspirin or P2Y₁₂ blockers before two weeks after bare-metal stenting or before six months after drug-eluting stenting is associated with a very high risk of thrombotic events.^[57,59,60,62,88] Finally, even the decision itself to proceed with percutaneous coronary intervention rather than to coronary artery bypass surgery should be taken carefully, as recent data suggest that surgery can provide significant clinical benefits

in patients with severe and diffuse coronary artery disease, especially if diabetic.^[75,89,90]

6 Reconciling the evidence

Based on the detailed appraisal of the available evidence stemming from as many as 18 studies and 1082 patients, the results of percutaneous coronary intervention in nonagenarians show high variability in patient selection, features, and results (Table 1).^[3,31,32,65,66,91–103] Most patients were male, they tended to present with ST-elevation myocardial infarction in 22% of cases, were almost all showing extensive multi-vessel disease, and were treated sparingly with drug-eluting stents. Yet, some studies reported drug-eluting stent usage in all nonagenarians.^[29,93,100]

Clinical results were accordingly highly variable, despite a median short-term mortality of 14% and a long-term case fatality of 18%. Indeed, some studies reported no early deaths,^[95,100,103] whereas other series showed an in-hospital, or one-month death rate reaching as high as 32%-34%.^[96,101] Notably, the long-term rate of major adverse cardiac events (usually defined as the composite of death, myocardial infarction, or target lesion revascularization) was not much higher than the long-term death rate alone, suggesting that in these patients restenosis does not seem to be a major clinical issue.

In summary, these findings and the totality of the evidence and experience data lead to the conclusion that percutaneous coronary intervention is feasible in carefully selected nonagenarians, provided that a number of

Table 1. Key studies reporting on percutaneous coronary intervention in nonagenarians.

Study	Patients	STEMI	DES	Short-term death	Long-term death	Long-term MACE
Antonsen (2012) ^[3]	109	100%	27%	26%	33%	NA
Chait (2011) ^[91]	90	27%	73%	8%	68%	NA
Danzi (2010) ^[31]	100	100%	NA	19%	32%	33%
From (2008) ^[92]	138	NA	35%	9%	71%	81%
Hendler (2011) ^[93]	45	31%	NA	11%	NA	NA
Ionescu (2010) ^[94]	13	100%	31%	23%	46%	NA
Kondur (2010) ^[95]	20	NA	NA	0	12%	NA
Koutouzis (2010) ^[96]	22	100%	NA	32%	32%	32%
LeBude (2012) ^[97]	21	NA	NA	0	NA	NA
Lee (2008) ^[65]	28	39%	100%	21%	39%	53%
Lemesle (2009) ^[66]	171	59%	60%	4%	11%	14%
Moreno (2004) ^[98]	26	27%	NA	19%	35%	NA
Sillano (2012) ^[32]	146	23%	24%	5%	38%	28%
Parikh (2009) ^[99]	32	19%	NA	9%	19%	19%
Rekik (2010) ^[100]	6	0	17%	0	0	33%
Salinas (2011) ^[101]	38	100%	16%	34%	NA	NA
Teplitsky (2007) ^[102]	65	22%	5%	14%	18%	21%
Wu (2004) ^[103]	12	20%	NA	0	25%	NA
Median (95% bootstrap confidence intervals)*	28 (6–65)	22% (0–39%)	17% (5%–100%)	14% (0–21%)	18% (0–39%)	33% (21%–53%)

*Based on 1000 bootstrap samples computed with SPSS 20 (IBM, Armonk, NY, USA). DES: drug-eluting stent; Long-term: 6-month to longer follow-up; MACE: major adverse cardiac event; MVD: multivessel disease or revascularization; NA: not applicable or available; Short-term: in-hospital to 1-month follow-up; STEMI: ST-elevation myocardial infarction.

evidence and experience-based recommendations are followed (Table 2). Adverse events are, however, common in these subjects with high rates of short as well as long-term death, unless only very fit patients are selected. Indeed, it can be argued that an initial price of procedural

risk has to be clearly offset by a credible long-term benefit on prognosis and, most importantly, quality of life and autonomy in order to make percutaneous coronary intervention in very elderly subjects risk-beneficial as well as cost-beneficial.

Table 2. Evidence- and experience-based recommendations for percutaneous coronary intervention in nonagenarians.

Management step	Recommendation	Elaboration
Triage	Measurement of troponin and brain natriuretic peptide levels, and early transthoracic echocardiography are recommended before PCI is envisioned	Systematic use of biomarkers and echocardiography enables more accurate risk-stratification and triage of patients, optimizing care by identifying those most likely to benefit from an early invasive approach
	Screening for co-morbidities reducing life expectancy or increasing the risk of complications is recommended before PCI	Co-morbidities may adversely impact on the in-hospital management and long-term outlook of the very elderly, and they should not be discovered after PCI but rather recognized and appraised beforehand
Diagnosis	Myocardial ischemia/infarction should be diagnosed with reasonable certainty before proceeding with PCI	Non-invasive diagnostic means (e.g., stress test) should be employed to reach a reliable diagnosis before coronary angiography and PCI to avoid performing unnecessary procedures
Access	Radial access is recommended for coronary angiography and PCI	Radial access reduces fatal and non-fatal complications in comparison to femoral access for diagnostic and interventional coronary procedures
Revascularization	Maximal medical therapy is recommended before PCI	Irrespective of the final decision on revascularization (PCI, CABG, or none), maximal medical therapy should be instituted to improve short-term and long-term prognosis
	A culprit-lesion only strategy for PCI is recommended in patients with multivessel disease	Multivessel disease is common in nonagenarians, and a culprit-lesion only revascularization strategy is more risk-beneficial than a multivessel stenting approach in case of diffuse disease associated with acute coronary syndromes
	Bare metal stents are recommended for PCI	Despite the theoretical benefits of drug-eluting stents, the superior safety profile of bare metal stents make them the 1 st choice coronary device in nonagenarians
	FFR, IVUS and OCT are recommended only in carefully selected patients	Functional assessment and invasive imaging techniques, while potentially useful in providing additional data on coronary artery disease severity and features, are not routinely recommended given their potential to increase the risk of peri-procedural adverse events
	Provisional main-branch stenting is recommended for bifurcation PCI	Coronary bifurcation lesions should be managed with a simple main-branch stenting approach as this is associated with similar efficacy but superior safety in comparison to a complex stenting approach
	Contrast media use should be minimized before and during PCI	The risk of contrast-associated nephropathy, potentially fatal if leading to acute renal failure, should be minimized by a cautious use of contrast (e.g., by limiting the total contrast volume or staging the procedures)
Ancillary therapy	Dual antiplatelet therapy with aspirin and clopidogrel is recommended after PCI	Dual antiplatelet therapy with aspirin and novel P2Y ₁₂ receptor blockers such as prasugrel and ticagrelor, while potentially more effective than one based on clopidogrel, does not appear sufficiently safe in nonagenarians
Supportive care	Rehabilitation is recommended after PCI	Rehabilitation may be associated with cardiac and non-cardiac favorable effects in the very elderly, enabling shorter hospital stays and a more autonomous lifestyle upon final discharge

CABG: coronary artery bypass grafting; FFR: fractional flow reserve; IVUS: intravascular ultrasound; OCT: optical coherence tomography; PCI: percutaneous coronary intervention.

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