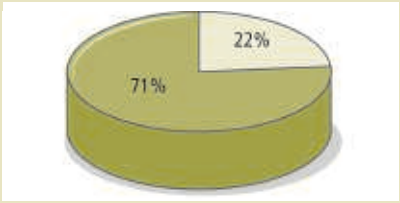
abstract




*The burden of cardiovascular disease increases significantly with age. One of the most complex decisions facing clinicians is whether or not to perform coronary revascularization in an older patient. Our review of recent evidence on revascularization therapies for aging patients with non-ST-elevation acute coronary syndromes found an inverse relationship between age and the use of evidence-based medications as well as revascularization procedures. Older patients undergoing revascularization had a higher likelihood of adverse outcomes compared with younger patients undergoing revascularization. However, older patients who underwent revascularization had significantly better outcomes than their counterparts who did not undergo revascularization, suggesting that they deserve the same consideration as younger patients in the use of coronary interventions.*

***Key words:*** *acute coronary syndromes, percutaneous coronary intervention, coronary artery bypass graft surgery, evidence-based medications, outcomes*

# The Role of Revascularization in Older Patients with Acute Coronary Syndromes

***Anna J.M. van de Sande, BSc,*** *Medical Student, Thoraxcenter, Erasmus Medical Center, Rotterdam, The Netherlands. Visiting Medical Student, Canadian VIGOUR Center, University of Alberta, Edmonton, AB.*

***Paul W. Armstrong, MD,*** *Professor, Division of Cardiology, Department of Medicine, University of Alberta, Edmonton, AB,*

***Padma Kaul, PhD,*** *Assistant Professor, Division of Cardiology, Department of Medicine, University of Alberta, Edmonton, AB.*

## Introduction

It is well documented that the burden of cardiovascular disease increases significantly with age. According to Alberta's Health and Wellness database (www.health.gov.ab.ca), between 1998 and 2002, older adults (age ≥ 65 years) accounted for approximately 10% of the overall population and for 30% of all hospital emergency department visits related to coronary syndromes (acute myocardial infarction [AMI], unstable angina, stable angina, and chest pain) in the province. Remarkably, however, older patients accounted for approximately 80% of all deaths in this population that occurred within 30 days of presentation (Figure 1).

One of the most complex decisions facing clinicians is whether or not to perform coronary revascularization in an older patient. Difficulty in making rational treatment decisions for older individuals is compounded by the limited evidence from clinical trials regarding the efficacy of different management strategies and on the impact of comorbidities on procedural outcomes in this high-risk population. The results of the Trial of Invasive versus Medical therapy in Elderly patients (TIME) trial, the first randomized trial of invasive versus medical therapy focussed entirely on patients over the age of 75 years, were equivocal, with revascularization benefits in quality of life outcomes and adverse events observed at six months dissipating by one year.[1–3] The preliminary report from the Senior Primary Angioplasty in Myocardial Infarction (SENIOR PAMI) trial comparing primary angioplasty versus fibrinolytic therapy among older patients with AMI found no mortality benefit associated with mechanical reperfusion.[4]

In a recent systematic review of the literature, Mehta *et al.* provided a comprehensive review of reperfusion strategies among older patients with AMI.[5] Our current review therefore focusses primarily on recent evidence regarding revascularization therapies for aging patients with non–ST-elevation acute coronary syndromes.

## Revascularization Rates among Older Patients

Prior studies have consistently documented lower rates of evidence-based treatments among older patients. Guigliano *et al.*, in 1991–1992, found both the use of evidence-based medications such as acetylsalicylic acid and beta-blockers as well as referral to cardiac catheterization to be inversely correlated with increasing age.[6,7] A decade later, revascularization rates continued to be significantly lower among older patients. In 2002, De Servi *et al.*[8] found that an aggressive strategy (coronary arteriography within four days of admission, followed by revascularization, if feasible) was adopted in 39% of older patients

compared with 56% of younger patients (p<0.001). An interventional procedure within 30 days was performed in 30% of older patients and 48% of younger patients (P<0.001). Similarly, data from the recent Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines (CRUSADE) National Quality Improvement Initiative show that older patients were more likely to be treated at smaller, nonacademic hospitals and less likely to be treated by cardiologists. The use of an early invasive strategy, defined as diagnostic coronary angiography within 48 hours of admission, attenuated with age starting around the age of 70 years. Only 40% of patients over age 70 underwent early invasive care, with the number decreasing to <20% in individuals past the age of 85 years.[9]

## Effect of Revascularization on Outcomes among Older Patients

Although outcomes among older patients undergoing revascularization have improved over the years, they continue to be significantly worse than those observed among younger patients.[10] In an examination of all patients undergoing percutaneous coronary intervention (PCI) between 1989 and 1993, Wennberg *et al.* found that PCIs in the older patients were more often performed in unstable syndromes compared with younger patients.[11] Among octogenarians, 83.2% of PCIs were performed for unstable syndromes. There was a statistically significant increase in risk of death after PCI with advancing age: those >80 years of age had more than an eightfold increase in post–PCI in-hospital death compared with those <60 years of age.

Similarly, Batchelor *et al.* found that octogenarians undergoing PCI have a two- to fourfold increase in risk of complications, including death (3.8% vs. 1.1%), stroke (0.58% vs. 0.23%), and Q wave MI (1.9% vs. 1.3%) compared with younger patients.[10] While the authors speculate that increasing use of stents may improve PCI outcomes in older adults, De Gregorio found significantly higher rates of procedural outcomes and significantly worse six-month mortality among older patients undergoing PCI with stents.[12]

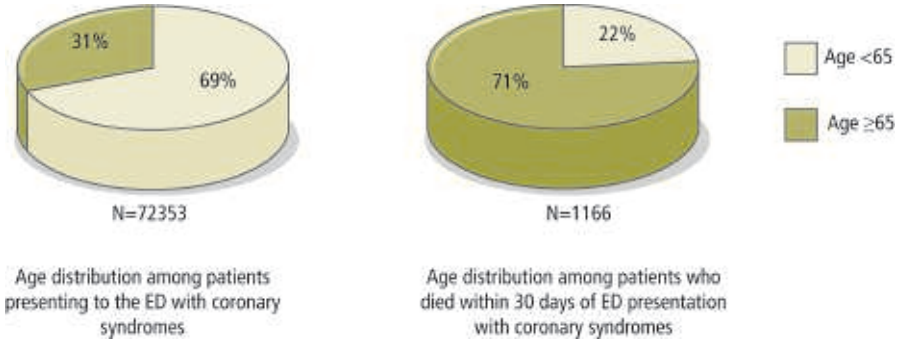
The higher mortality among aging revascularized patients may to some extent be driven by increased use of coronary artery bypass surgery. Liistro *et al.* found that older patients with non-ST elevation MI undergoing revascularization had a significantly higher overall mortality, cardiac mortality, and death plus myocardial infarction compared to younger patients after 10 months of follow-up.[13] Although not statistically significant, the rate of stroke was also higher among older patients (1.2% vs. 0.7%). The authors found that the difference in cardiac death between the two age groups was related to a greater proportion of older patients being treated with coronary artery bypass grafting.[13]

## Medical versus Revascularization Therapy in Older Patients

Although older patients undergoing revascularization appear to have worse outcomes compared with younger patients, they appear to have better mortality outcomes and symptom relief compared with older patients who do not undergo revascularization. Given the high morbidity and mortality associated with conservative therapy, some studies have even reported a greater absolute risk along with either similar or larger relative risk reduction in older individuals compared to the younger patients. Figure 2 (top panel) provides a summary of the relative risk associated with aggressive versus conservative management among older patients with non–ST-elevation acute coronary syndromes. Among the 2,220 patients enrolled in the Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy-Thrombolysis in Myocardial Infarction (TACTICS-TIMI) 18 trial, 43% were 65 years of age or older.[14] Among these patients, the early invasive strategy yielded an absolute reduction of 4.8 percentage points (8.8% vs. 13.6%; P = 0.018) and a relative reduction of 39% in death or MI at six months. Among the patients older than 75 years of age, the early invasive strategy conferred even an absolute reduction of 10.8 percentage points (10.8% vs. 21.6%; P = 0.016) and a relative reduction of 56% in death or MI at six months.

In the Fast Revascularisation during InStability in Coronary artery disease (FRISC II) invasive trial, 52% of all patients that were enrolled were 65 years or older. There was a significant reduction in death, myocardial infarction, or both at six months (RR=0.66, 95% CI 0.50–0.89) and symptoms of angina at six months (RR=0.53, 95% CI 0.44–0.64) in older patients who underwent invasive therapy than in those who received medical therapy.[15] After one year of follow-up there was still a significant reduction in death,

**Figure 1:** Proportion of Older and Younger Patients Presenting to the Emergency Department (left panel); Proportion of 30-day Deaths Accounted for by Older Patients (right panel)




Source: Alberta Health and Wellness database (www.health.gov.ab.ca).

myocardial infarction, or both (RR=0.63, 95% CI 0.48–0.83) in patients who were 65 years or older.

The Randomized Intervention Trial of unstable Angina (RITA)-3 also found a reduction in refractory or severe angina for patients who were assigned to interventional therapy compared with patients who were assigned to medical therapy after one year of follow-up. There was no significant difference in death or myocardial infarction. After subgroup analysis, age did not seem to influence the outcome.[16]

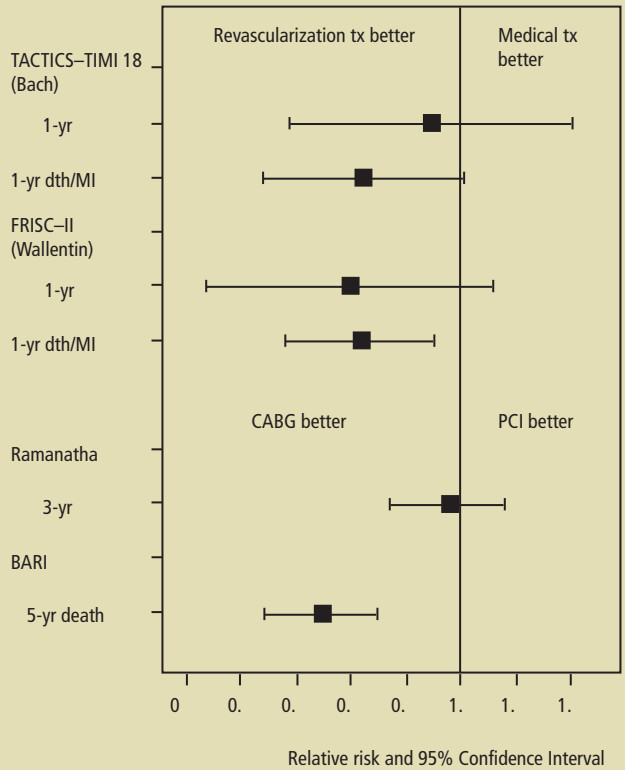
## PCI versus CABG for Older Patients

The relative risks associated with coronary artery bypass grafting (CABG) versus PCI in older adults are summarized in Figure 2 (bottom panel). The Bypass Angioplasty Revascularization Investigation (BARI) randomized trial showed that patients 65 years or older had less recurrent angina and were less likely to undergo repeat procedures after revascularization compared to younger patients.[17] The investigators found that CABG resulted in a greater relief of angina and fewer repeat procedures than patients who underwent PCI. This trial also showed significantly better survival rate in patients 65 years or older who underwent CABG than in patients who underwent PCI after five years of follow-up (85.7% and 81.4% respectively).

In contrast, the Angina With Extremely Serious Operative Mortality Evaluation (AWESOME) study, which compared long-term survival of PCI with CABG for the treatment of patients with medically refractory myocardial ischemia and at least one additional risk factor for an adverse outcome, found no significant difference in 36-month survival rates among older patients (age > 70) who underwent bypass versus percutaneous intervention.[18]

There is limited evidence on the efficacy of emerging health technologies among older patients. One of the few studies that examined this issue (by Demaria *et al.*) found a better outcome in operative mortality and stroke in octogenarians with off-pump coronary artery bypass grafting surgery (OPCAB) compared to cardiopulmonary bypass (CPB).[19] Approximately 94% of the patients in this registry with CPB and 90% of the patients with OPCAB had unstable angina. The operative mortality was 15.9% in the CPB group and 4.8% in the OPCAB group (P=0.004). There were four postoperative strokes (6.3%) in the CPB group and none (0%) in the OPCAB group (P=0.004). The type of surgery (CPB or OPCAB) was also an independent predictor of operative mortality and stroke (OR=4.171).

**Figure 2:** Relative Risks Associated with Revascularization among Older Patients




## Conclusion

Although older adults represent the fastest-growing population segment in North America and face the greatest risk of coronary disease, few randomized clinical trials have examined the efficacy of cardiovascular therapies among this age group. In fact, older adults have historically been under-represented in randomized controlled trials examining the efficacy of new cardiovascular therapies.[20,21] As documented by Lee *et al.*, patients aged 75 years or older accounted for 2% of all patients enrolled in acute coronary syndrome clinical trials between 1960 and 1990.[20] In more recent trials (patients enrolled after 1995) the percentage has increased to 13% but continues to figure well below the estimated 50% of older women and 70–80% older men with the disease.[21–24] The issue of generalizing results observed in clinical trials to the broader population of patient is also a concern. There is evidence to suggest that Canadian patients enrolled in clinical trials are more often male and have less comorbid disease.[25] With these caveats in mind, evidence from observational studies suggests that older patients have a lower likelihood of undergoing revascularization procedures and a higher likelihood of adverse outcomes compared with younger patients. However, among aging patients, revascularization (either PCI or CABG) appears to be associated with better outcomes compared with more conservative therapy, thereby suggesting that these patients deserve the same consideration as younger patients in the use of coronary interventions.

Dr. Kaul is supported by the Canadian Institutes for Health Research (CIHR) and the Alberta Heritage Foundation for Medical Research (AHFMR).
No competing financial interests declared.

## Key Points

Evidence from clinical trials on the efficacy of different management strategies and the impact of comorbidities on procedural outcomes for coronary syndromes is limited in the older population.

The use of evidence-based medications such as acetylsalicylic acid and beta-blockers, referral to cardiac catheterization, and revascularization rates attenuate with increasing age.

While aging patients' revascularization (either PCI or CABG) outcomes compare unfavourably to younger adults, they appear to have better mortality outcomes and symptom relief compared with older patients who do not undergo revascularization.

The number of patients aged 75 years or older enrolled in acute coronary syndrome clinical trials remains low but has increased in the last ten years, which will ultimately yield valuable information about this population segment.

## References


1. TIME Investigators. Trial of invasive versus medical therapy in elderly patients with chronic symptomatic coronary-artery disease (TIME): a randomised trial. Lancet 2001;358:951–7.
2. Pfisterer M, Buser P, Osswald S, et al. Outcome of elderly patients with chronic symptomatic coronary artery disease with an invasive vs optimized medical treatment strategy: One-year results of the randomized TIME trial. JAMA 2003;289:1117–23.
3. Pfisterer M; Trial of Invasive versus Medical therapy in Elderly patients Investigators. 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;110:1213–18.
4. Grines C. SENIOR PAMI. A prospective randomized trial of primary angioplasty and thrombolytic therapy in elderly patients with acute myocardial infarction. TCT 2005; October 16–21, 2005; Washington, DC.
5. Mehta RH, Granger CB, Alexander KP, et al. Reperfusion strategies for acute myocardial infarction in the elderly: benefits and risks. J Amer Coll Cardiol 2005;45:471–8.
6. Braunwald E, Mark DB, Jones RH, et al. Clinical practice guideline number 10 (amended): Unstable Angina: Diagnosis and Management. Rockville, MD: US Dept of Health and Human Services, Agency for Health Care Policy and Research and the National Heart, Lung, and Blood Institute; Public Health Service; May 1994. AHCPR publication 94-0602.
7. Giugliano RP, Camargo CA,Jr, Lloyd-Jones DM, et al. Elderly patients receive less aggressive medical and invasive management of unstable angina: Potential impact of practice guidelines. Arch Intern Med. 1998;158:1113–20.
8. De Servi S, Cavallini C, Dellavalle A, et al. Non-ST-elevation acute coronary syndrome in the elderly: Treatment strategies and 30-day outcome. Am Heart J 2004;147:830–6.
9. Alexander KP, Roe MT, Chen AY, et al. Evolution in cardiovascular care for elderly patients with non-ST-segment elevation acute coronary syndromes: Results from the CRUSADE national quality improvement initiative. J Am Coll Cardiol 2005;46:1479–87.
10. 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;36:723–30.
11. Wennberg DE, Makenka DJ, Sengupta A, et al. Percutaneous transluminal coronary angioplasty in the elderly: epidemiology, clinical risk factors, and in-hospital outcomes. The northern New England cardiovascular disease study group. Am Heart J 1999;137:639–45.
12. De Gregorio J, Kobayashi Y, Albiero R, et al. Coronary artery stenting in the elderly: Short-term outcome and long-term angiographic and clinical follow-up. J Am Coll Cardiol 1998;32:577–83.
13. Liistro F, Angioli P, Falsini G, et al. Early invasive strategy in elderly patients with non-ST elevation acute coronary syndrome: Comparison with younger patients regarding 30 day and long term outcome. Heart. 2005;91:1284–88.
14. Bach RG, Cannon CP, Weintraub WS, et al. The effect of routine, early invasive management on outcome for elderly patients with non-ST-segment elevation acute coronary syndromes. Ann Intern Med. 2004;141:186–95.
15. Wallentin L, Lagerqvist B, Husted S, et al. Outcome at 1 year after an invasive compared with a non-invasive strategy in unstable coronary-artery disease: The FRISC II invasive randomised trial. FRISC II investigators. fast revascularisation during instability in coronary artery disease. Lancet 2000;356:9–16.
16. Fox KAA, Poole-Wilson PA, Henderson RA, et al. Interventional versus conservative treatment for patients with unstable angina or non-ST-elevation myocardial infarction: the British Heart Foundation RITA 3 randomised trial. Lancet 2002;360:743–51.
17. 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.
18. 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;80:1340–6.
19. Demaria RG, Carrier M, Fortier S, et al. Reduced mortality and strokes with off-pump coronary artery bypass grafting surgery in octogenarians. Circulation 2002;106(Suppl 1):S5–10.
20. Lee PY, Alexander KP, Hammill BG, et al. Representation of elderly persons and women in published randomized trials of acute coronary syndromes. JAMA 2001;286:708–13.
21. Gurwitz JH, Col NF, Avorn J. The exclusion of the elderly and women from clinical trials in acute myocardial infarction. JAMA 1992;268:1417–22.
22. American Heart Association. Heart disease and stroke statistics – 2003 update. Available online at http://www.americanheart.org/. Accessed April 15, 2006
23. Health Canada. The changing face of heart disease and stroke in Canada 2000. Available online at http://www.hc-sc.gc.ca/. Accessed April 15, 2006
24. Williams MA, Fleg JL, Ades PA, et al. Secondary prevention of coronary heart disease in the elderly (with emphasis on patients ≥ 75 years of age) An American Heart Association scientific statement from the council on clinical cardiology subcommittee on exercise, cardiac rehabilitation and prevention. Circulation 2002;105:1735?43.
25. Jha P, Deboer D, Sykora K, et al. Characteristics and mortality outcomes of thrombolysis trial participants and non-participants: a population-based comparison. J Am Coll Cardiol 1996;27:1335–42.