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Editorial

Management of Non-ST-Elevation Myocardial Infarction in Elderly Patients: Time to Consider Frailty and Quality of Life

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See article by Saraswat et al., pages 274–280 of this issue.

Advancing age is an independent and unmodifiable risk factor for the development of coronary artery disease.[1] Consequently, the prevalence of coronary artery disease for Canadians aged 75 years and older is high, standing at over 30% in 2016.[2] As the population ages with the baby boomer generation the prevalence of coronary artery disease will also increase. According to Statistics Canada, the population aged 75 years and older grew at nearly 3 times the rate of the overall population between 2012 and 2016.[3]

The treatment of coronary artery disease has greatly improved over the past decades, and combined with better risk factor control has resulted in the well documented effects of decreasing coronary artery disease-related morbidity and mortality.[4] Although it might be assumed that these benefits apply equally across the full age spectrum it must be remembered that relatively few patients older than the age of 75 years were included in these studies. Therefore, an important question is whether older patients are deriving the same benefits to reduce coronary artery disease mortality and morbidity that have been reported in these studies?

Elderly patients have long been known to receive less evidence-based treatment than their younger counterparts—perhaps because they have often been excluded from clinical trials in the past.[5] Recent studies, however, suggest that evidence-based treatment for elderly patients is increasing, and improving outcomes. A recent registry from England and Wales containing 616,011 acute coronary syndrome (ACS) events from 2003 to 2010 analyzed mortality and evidence-based therapy for patients aged 75 years and older.[6] The overall in-hospital mortality for patients aged 75-84 years who present with non-ST-segment elevation myocardial infarction (NSTEMI) decreased from 19.6% to 10.6% for these years. For patients 85 years of age and older the rate decreased from 31.5% to 20.4%. Although these are encouraging findings, it is important to realize that the in-hospital mortality rate for NSTEMI patients is $>$ 10 times higher for patients 75-84 years old and $>$ 18 times higher in those 85 years of age and older compared with patients younger than 55 years old. Evidence-based treatments also increased significantly over the registry follow-up.

The effect of early invasive therapy with angiography and revascularization as needed to reduce cardiac events must be considered in the elderly population. There is some support for an early invasive approach on the basis of guideline recommendations. The 2014 American Heart Association/American College of Cardiology guidelines give a class Ia recommendation for early invasive therapy in NSTEMI-ACS patients aged 75 years and older.[7] A similar recommendation is given in the 2016 European Society of Cardiology guidelines but with a more conservative class IIa rating.[8] Although there might be some question about the benefit of an invasive approach in the elderly patient, it should be remembered that this group is at the greatest risk and that life expectancy is increasing in the elderly population. For instance, between 2002-2004 and 2012-2014, the average life expectancy of an 80-year-old Canadian has increased from 9 years to 10 years.[9] This gives ample rationale for an NSTEMI-ACS treatment that could help quality of life and life expectancy in elderly patients.

In this issue of the *Canadian Journal of Cardiology*, Saraswat et al.[10] present a systematic review and meta-analysis of trials comparing invasive with conservative treatment for patients aged 75 and older who present with NSTEMI. In this study invasive therapy was defined as the routine use of angiography for all NSTEMI presentations. The conservative therapy was defined as treatment with medical therapy and the use of angiography only with recurrence of symptoms or

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recurrent evidence of ischemia on electrocardiogram. There was a significant reduction in mortality at 30 days (odds ratio [OR], 0.50; 95% confidence interval [CI], 0.33-0.75; $P = 0.0009$) and 12 months (OR, 0.45; 95% CI, 0.34-0.59; $P < 0.00001$) for the invasive group compared with the conservative group. There was significant heterogeneity observed in the analyses. When the subgroup analyses were done comparing the randomized controlled trials (RCTs) with observational studies it was reported that mortality benefits for an early invasive approach at 30 days and 12 months were only because of the observational studies. Observational studies are subject to selection bias, because clinicians tend to select patients with favourable characteristics and to suggest more conservative care for the very old or frail patients. When only RCTs were analyzed, mortality benefits could not be detected for the early invasive approach at either 30 days or 1 year, although there were power issues for that outcome regarding sample sizes.

The RCTs did show a reduction in reinfarction rate at 12 months for early invasive therapy compared with conservative therapy (OR, 0.47; 95% CI, 0.32-0.70; $P = 0.0001$). There were also significantly fewer strokes in the early invasive group. Major bleeding was significantly greater in the early invasive group although the rate of bleeding was low in both groups. The assumption by the authors was the higher bleeding rate in the invasive group was access site bleeding.

So what do we learn from this study and how should this information be used in clinical practice? The benefits of the early invasive approach seem to outweigh the risks for patients in this age group, because we are confident that an early invasive approach will reduce reinfarction rates at 12 months, and will probably reduce stroke risk. This might be associated with a greater risk of major bleeding, although the absolute rate of bleeding is low and thought to be related to the access site. The use of a radial artery approach for the invasive treatment could potentially reduce the risk of bleeding. We do not know for certain that an early invasive approach reduces mortality in these patients. Although the observational studies would support a mortality benefit for the early invasive approach, the RCTs do not corroborate these findings. However the individual RCTs were not powered to assess these outcomes and even if the RCT data are pooled there is probably a lack of power. It should be mentioned that although not significant, the point estimate for mortality at 12 months for the RCTs did trend in the direction of benefit for early invasive therapy.

After this review, three very important questions remain unanswered:

First, what about quality of life? Many older patients will care much less for length of life in numerical terms, compared with the quality of that time. In stable angina patients, the **T**rial of **I**nvasive vs **M**edical Therapy in **E**lderly Patients (TIME) study has shown better quality of life and function in older patients with angina after 6 months if they underwent invasive therapy.[11] This advantage, however, dissipated at 1 year and at 4 years.[12,13]

Second, is there an age group in which the benefits diminish? We all know that treating a healthy 75-year-old patient is much different from treating a healthy 95-year-old patient. In an RCT of NSTEMI patients age 80 years and older by Tegn et al., the observed benefits in the composite outcome (which was mainly driven by reinfarction and need for revascularization) seemed to decrease with age when analyzed using logistic regression.[14] After age 90 years, there seemed to be a reversal of the treatment effect, although the study was not adequately powered to conclusively make that statement.

Third, there needs to be a consideration of frailty, or "biological age." Many data show worse clinical outcomes with frailty. Frail patients are also less likely to receive angiotensin-converting enzyme inhibitors and β-blockers.[15] Does this mean that frail patients should be treated more aggressively, because they have higher baseline risk? Or does it rather mean that frail patients, because they are more likely to experience adverse effects from medical and interventional therapy, should be treated more conservatively? Should therapies directed at improving frailty be instituted in NSTEMI-ACS patients? Collaborative care including the cardiologist, the primary care provider, and a geriatrics team can be of great benefit to selected frail older patients with medical complexity.[16]

We are left with a conclusion that is very familiar to those involved in elder care. One-size-fits-all decision trees do not exist and care must be individualized with regard to the patient's goals, comorbid conditions, overall health, and cognitive status. Thus, at this juncture decisions will still be made on a case-by-case basis. There is a need for an RCT to explore the effects of early invasive therapy in this patient population, especially one that takes into account frailty and quality of life. In the meantime, studies like those by Saraswat et al.[10] inform us that an early invasive approach is probably preferable in patients aged 75 and older because of the reinfarction and stroke risk benefit, although there remains a doubt about the mortality benefit of the intervention.

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