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## Hotline Editorial

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# TIME has come to have a closer look at the management of cardiovascular disease in the elderly

Individuals older than 75 years represent the fastest-growing population segment in the western world. Coronary artery disease is the leading cause of morbidity and mortality in men as well as women in this age group. Contrary to younger individuals, rates of coronary artery disease continue to increase in the elderly and more than one third of health-care expenditures are spent on them<sup>[1]</sup>. Therefore, the evaluation of optimal management strategies in elderly patients with symptomatic CAD is important not only for the individual, but also for society in view of health care cost.

Randomized studies comparing coronary artery bypass grafting (CABG) or percutaneous coronary interventions with medical therapy in patients with chronic coronary artery disease have shown that revascularization provides symptom relief and improves survival in certain high risk subsets. Most of these were mortality trials, average age of participating patients was around 65 years and inclusion was based on 'suitable' coronary anatomy. In general, elderly patients are severely under-represented in randomized trials evaluating different treatment modalities for coronary artery disease<sup>[2]</sup>. The same holds true for heart failure, another important cardiovascular problem in advanced age. As compared to their younger counterparts, important differences have to be taken into consideration in elderly patients with coronary artery disease: symptom presentation may be different, complex coronary vessel pathology, comorbid conditions and psychosocial disorders are more prevalent, tolerance to drugs is variable, side effects are more frequent and more severe, and the risk of invasive procedures is generally increased. Therefore, safety and efficacy of cardiovascular therapies may differ between elderly and younger patients and therapeutic goals may not be the same. In contrast to younger patients, the primary goal of treatment in elderly patients may no longer be prolongation of life but rather improvement in quality of life (QOL). To provide evidence-based treatment for coronary artery disease in the elderly, clinical trials designed specifically for this age group are urgently needed.

Traditionally, percutaneous coronary interventions and CABG have been offered only reluctantly to elderly patients for fear of high risk at only modest benefit. With improvement of interventional and surgical techniques in recent years, success rates have increased and complication rates decreased especially in elderly patients. Several retrospective registry reports on revascularization in elderly patients have shown that CABG<sup>[3]</sup> and percutaneous coronary interventions<sup>[4]</sup> can be achieved with an acceptable risk in selected patients, but that the frequency of in-hospital complications and mortality is higher compared with younger patients. The findings of these reports were based on patients referred for such interventions with suitable coronary anatomy and may therefore not represent 'real world' elderly patients with coronary artery disease and chest pain as seen frequently in outpatient clinics or by practicing physicians.

The Trial of Invasive versus Medical Therapy in the Elderly (TIME) addressed the management of elderly patients with chronic angina refractory to standard drug therapy<sup>[5]</sup>. Three hundred and five patients aged 75 years or older with chronic angina Canadian Cardiac Society class II or more despite at least two antianginal drugs were included in this prospective randomized multicentre trial. An invasive strategy including coronary angiography and, if possible, revascularization with percutaneous coronary interventions or CABG surgery was compared to a strategy with optimized medical therapy. The primary end-point was quality of life after 6 months as assessed by questionnaire and the composite outcome of death, non-fatal myocardial infarction and hospital admission for acute coronary syndrome with or without the need for revascularization. The average age of the study population was 80 years and almost half were female. Study patients had a high coronary risk profile and more than half had significant co-morbid conditions. Coronary angiograms in the invasive group showed multivessel disease in 79% and no significant coronary stenoses in 7% of patients. A revascularization procedure was performed in 74% of patients in the invasive group who were catheterized,

whereas in the remaining 26% it was refused (7%), not possible (12%) or not necessary (7%). In the optimal medical group, antianginal medication was increased by a mean of 0.8 drugs per patient with additional increases in drug dosages in 55% of patients. During follow-up, angina severity decreased and all indices of quality of life improved significantly in both groups, although the improvements were greater in patients of the invasive group. Major adverse cardiac events occurred in 19% of patients in the invasive and 49% of patients in the medical group ( $P < 0.0001$ ). This difference was mainly due to higher rates of hospital admissions for acute coronary syndromes and for non-fatal myocardial infarctions in the medical group. A third of patients in this group needed revascularization for uncontrolled symptoms during follow-up. The 6-month mortality rate was low overall (6.3%), but it was twice as high in the invasive vs the medical group. However, half the cardiac deaths in the invasive group occurred in patients unwilling or unsuitable for revascularization. The revascularization mortality was only 2.5%. In summary, this trial showed that patients aged 75 years or older with angina despite standard treatment benefit from optimized medical therapy and even more from revascularization in terms of symptom relief and quality of life. These patients should not be denied invasive assessment if clinically indicated despite their age and high-risk profile. If coronary anatomy is suitable for revascularization, this treatment should be offered but patients have to be aware of a small peri-interventional mortality hazard.

There are several unique points in this study which may be stressed: first, patients were randomized based on their clinical presentation as in a practice setting and not based on angiographic findings as in previous reports in younger patients. This led to a 7% rate of patients without significant coronary artery disease, mostly women (15% vs 1% in men) and to 12% of patients with no suitable anatomy for any revascularization. Maybe at least some of the former could have been identified by non-invasive testing which was not mandatory in this study. For routine practice this may indicate (1) that non-invasive testing, for instance with myocardial perfusion scintigraphy combined with pharmacological stress testing may have a role at least in elderly women with chronic angina and (2) that only about one out of eight patients in this age group will have a coronary anatomy not suitable for revascularization.

Second, invasively managed patients were revascularized either by percutaneous coronary interventions or CABG based on the judgement of the local investigators. Despite multivessel disease in 79% of patients, two-thirds were treated by percutaneous

coronary interventions which therefore contributed importantly to the beneficial outcome in angina severity and quality of life. This implies, on the other hand, that not all patients received full revascularization, a finding which was true for CABG surgery, too. It will be up to a separate detailed analysis to identify factors influencing the choice of revascularization mode and the relation between recurrent symptoms and outcome to the completeness of revascularization. In addition, such an analysis will indicate whether it was harmful to postpone revascularization in one third of medically managed patients who received it due to uncontrolled symptoms during the follow-up only.

Third, medical management was quite intense in all patients already at the start of the study, indicating that their symptoms were what some might call 'refractory'. Still, there was room for improvement as shown in medically treated patients which meant the addition of at least one drug in 80% and increases in dosages in more than half the patients. This led to a significant improvement of symptoms and quality of life; furthermore, two-thirds of medically managed patients did not need to undergo invasive evaluation and therapy. There is, to our knowledge, no prospective study in the literature documenting the beneficial effect of combined drug therapy in a similar manner<sup>[6]</sup>. This finding is therefore an important message from the TIME study too. It is remarkable that there is very little data except for relatively small subgroup analyses of medical therapy also for hypercholesterolaemia, hypertension or heart failure in elderly patients, including lipid-lowering and ACE-inhibitor therapy<sup>[7-9]</sup>.

Finally, the primary end-point of this trial was quality of life and not mortality. Quality of life is of utmost importance, particularly in elderly patients, and needs to be addressed appropriately. As expected, there was some discrepancy between quality of life and mortality in this trial, at least early on. Whereas quality of life improved significantly more in invasive as compared to medically managed patients, early mortality was twice as high in the invasive group. Although this mortality difference was statistically not significant and not directly related to revascularization procedures, it may reflect the increased risk of revascularization in elderly patients in general. Overall mortality was low in both groups and compared favourably to the mortality of the Swiss population of the same age in general: 6.3% in study patients versus 2.3% of 65-79 and 11.5% of >80-year-old Swiss subjects<sup>[10]</sup>. It will be important to see whether this early intervention hazard will be followed by a later survival benefit, as noted in other revascularization studies of high risk patients<sup>[11]</sup>.

Many unresolved issues remain in the management of elderly patients with cardiovascular disease. Risk factor management and treatment options in acute coronary syndromes are two problems where clinical research is badly needed. Besides coronary disease, the most prominent example is heart failure. In the last 15 years, major and successful efforts have been undertaken to improve morbidity and mortality from heart failure. As in coronary disease, elderly patients represented only a small minority of patients studied despite being mainly affected by this problem. Hopefully, the results of ongoing and planned work will soon allow evidence-based management of cardiovascular disease in elderly patients, too, taking into consideration all special aspects of the aged population.

**P. RICKENBACHER<sup>1</sup>**

**M. PFISTERER<sup>2</sup>**

<sup>1</sup>*Divisions of Cardiology,  
Medical University Clinic,  
Kantonsspital Bruderholz;*

<sup>2</sup>*University Hospital,  
Basel, Switzerland*

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