Stable angina in the elderly: diagnostic and therapeutic approach
Niccolò Marchionni\textsuperscript{a} and Francesco Orso\textsuperscript{b}

Introduction
In Western countries, ischemic heart disease is the leading cause of death, and stable angina is its frequent manifestation, representing the onset symptom in 50\% of the patients. When stable angina is present, the risk of adverse cardiovascular events doubles,\textsuperscript{1} and increases with age. It is estimated that in the United States of America 7 million patients are affected with stable angina, and the prevalence increases in the elderly reaching almost 10\% in patients over 85 years.\textsuperscript{2} The diagnosis of angina could be challenging in the elderly because of their comorbidities, functional limitations and the often atypical presentation of the symptoms. Accordingly, oldest patients with a clinical suspect of stable angina require an integrated diagnostic assessment starting with a careful clinical history and accurate physical exam, and extending to personalized laboratory and instrumental tests chosen considering the individual patient’s clinical and functional status. The clinical history, for instance, should be collected not only from the patient, but also from the family members or the direct caregiver. An accurate history is critical in the diagnostic process, for the frequent lack of typical symptoms leads to a delayed or even a missed diagnosis. The typical effort-induced pain, with rapid regression with rest, is often absent in the elderly, presenting rather, and more so with advancing age, atypical symptoms or angina equivalents such as dyspnea, jaws pain, nausea and epigastric pain. Furthermore, the diagnosis could be delayed by comorbidities limiting patient’s functional capacity such as neurologic (previous stroke, Parkinson’s disease) or osteoarticular conditions (osteoarthritis), which may contribute to hide effort-induced symptoms. The missed or delayed diagnosis increases the risk of adverse cardiovascular events, with higher incidence of acute coronary syndrome, heart failure or sudden death.

The physical exam should include a systematic search for signs of widespread atherosclerosis: absence of peripheral pulses, vascular murmurs, pressure gradients between the upper extremities, and an abnormal ankle/arm pressure index. Even when facing patients with typical symptoms, these signs suggest the need for further testing. Laboratory exams should evaluate the glycemic/metabolic and lipid profile and outline the risk factors previously undetected or inadequately controlled, as well as rule out anemia, very frequent and multifactorial in the elderly, and responsible for mismatch myocardial ischemia.

A 12-leads ECG should always be part of baseline assessment, albeit often of difficult interpretation for the presence of pacemaker, intraventricular conduction delays or left ventricular (LV) hypertrophy secondary to long-standing hypertension. These baseline ECG abnormalities, which are more frequent as age advances, could determine a false positive result of the stress test; on the other hand, functional limitations and reduced exercise tolerance can cause a falsely negative result. Notwithstanding these limitations, the current European Society of Cardiology stable angina guidelines recommend exercise stress test as first-level evaluation in elderly patients with suspected ischemic heart disease, and imaging pharmacologic stress test for patients unable to sustain an adequate physical effort.\textsuperscript{3} Jeger et al.\textsuperscript{4} demonstrated that patients over 75 years of age with a negative stress test, while on optimal medical treatment, had an excellent 1-year prognosis.

During the last few years, a minimally invasive technique, coronary computed tomography angiography, has been introduced as a novel method aiming at providing detailed coronary anatomical information. On the contrary, this test is not recommended in the elderly and very elderly patients, in whom extensive coronary calcifications impair its predictive value, due to the significant risk of falsely positive results. This test, because of its high negative predictive value, should be recommended for younger patients with low pretest probability of ischemic heart disease, to rule out the diagnosis.\textsuperscript{5} Elderly patients with myocardial ischemia proven by noninvasive testing should have the same access to optimal medical therapy and coronary angiography as younger individuals. It must be kept in mind, though, that patients over 80s present more often with high risk coronary lesions, such as left...
main disease, and have a higher incidence of complications after invasive procedure, such as contrast-induced nephropathy and vascular access problems, which are only partially decreased by measures such as preprocedural hydration and smaller doses of contrast medium, and resorting to radial rather than femoral artery access.

In this regard, the recommendation for coronary angiography in the very elderly should be based not only on symptoms or provocative testing, but be the result of multidimensional evaluation that takes into account the risk/benefit of the procedure, the presence of comorbidities, patient's cognitive profile, functional autonomy and quality of life, as well as his/her tolerance to optimal medical therapy. Regardless of chosen strategy, conservative vs. invasive, the treatment of stable angina in these patients should begin with life style modification and optimization of medical treatment. The goals of medical therapy are, in fact, symptoms improvement and prevention of adverse events. Accordingly, various classes of drugs could safely be prescribed to the elderly:

1. **Nitrates**: They improve angina symptoms through coronary arterial and venous vasodilatation, with increased coronary flow and reduced preload. Although the short acting nitrates are undoubtedly effective in improving angina symptoms, their chronic use is debated due to the frequent development of tolerance and to their negative effect on endothelial dysfunction. Furthermore, in the very elderly, caution should be used for the risk of severe orthostatic hypotension leading to syncope and falls. This risk is particularly evident when phosphodiesterase inhibitors for erectile dysfunction are used, and the patient should always be advised about the danger of this interaction.

2. **Beta-blockers**: Their antiangina action is brought by their negative chronotropic and inotropic effect, as well as afterload reduction that are the three main determinants of myocardial oxygen consumption. Caution should be taken in prescribing these drugs to older patients with sinus node dysfunction and A-V conduction abnormalities. Comorbidities such as diabetes and chronic obstructive pulmonary disease were previously considered as contraindication to these drugs, but beta-1 selective blockers, like bisoprolol, have been shown to be safe and well tolerated even in these patients. Not recommended in the very elderly is the association of beta-blockers and nondihydropyridine calcium antagonist (diltiazem or verapamil).

3. **Calcium antagonist**: They act through vasodilation and reduction of peripheral resistance, and the nondihydropyridinones also via a negative chronotropic and inotropic effect. Overall, they are a heterogeneous class of drugs, with vascular selective compounds (dihydropyridinic: amlodipine, nifedipine, felodipine), and other reducing heart rate (verapamil, diltiazem). The former drugs have the same risk as nitrates to induce hypotension, and the latter could have a negative inotropic effect, as well as negative chronotropic and dromotropic effect (particularly when used in association with beta-blockers), and can cause constipation – to the point of development of fecal impaction – or urinary retention in older patients with prostatic hypertrophy.

4. **Ivabradine**: This is a negative chronotropic drug acting by selective inhibition of the If current in the sinoatrial node, without affecting contractility or blood pressure. The drug has been initially approved by the European Medicine Agency (EMA) for the treatment of stable angina in patients not tolerating or not responding optimally to beta-blockers. The higher benefit, though, is achieved when used in association with beta-blockers, and this drug combination is generally well tolerated in the elderly.

5. **Ranolazine**: Is an inhibitor of the late sodium current with antiischemic and metabolic effects. In 2009, EMA approved ranolazine for use in patients with stable angina not adequately controlled by first-line drugs (beta-blockers and dyhydropyridinic calcium antagonists).

During the last 40 years, many studies – both randomized clinical trials and registries – compared conservative and invasive strategies for their effect on prognosis of patients with chronic ischemic heart disease and outlined the anatomical (left main disease, three vessels disease) or functional (extent of ischemic area, LV function) characteristics portending to an advantage of one treatment over the other. The first trials conducted during the 80s, Veteran Administration Study, the Coronary Artery Surgery Study and the European Cooperative Surgery Study (ECSS) compared surgical revascularization and medical treatment (basically, aspirin, nitrates and beta-blockers in about 50% of patients) and obtained controversial results: prognosis was similar with the two strategies in the first two studies, whereas 5-year mortality was better for surgical approach in the ECSS trial. These studies, albeit with their limitations, could identify high-risk patients, in particular those for whom surgical revascularization was clearly superior (e.g. patients with left main disease), who were then excluded from further trials because of ethical reasons. In these studies, elderly patients were underrepresented or even absent, considering that the ECSS study included only patients younger than 65 year. Over the following years, medical therapy has evolved as a result of pathophysiological advances bringing the discovery and clinical application of new drugs, so that the comparison between the two strategies could be tested, in more recent trials, with use of ‘optimal’ medical treatment. The Clinical Outcomes Using Revascularization (COURAGE) trial, randomized patients with Canadian Class I–III angina, a large portion of whom with evidence of ischemia, to percutaneous coronary intervention (PCI) and intensive medical treatment vs. intensive medical treatment.
treatment alone, and the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI-2D) trial, randomizing diabetic patients asymptomatic or with limited angina and evidence of ischemia, to revascularization by means of PCI or coronary artery by-pass grafting (CABG) vs. medical therapy; both trials failed to demonstrate an advantage of the revascularization strategy over the conservative medical treatment. Both trials, however, had significant limitations: the use of drug-eluting stents was very limited (2.7% in the COURAGE and 1/3 in the BARI-2D), and there was high number of cross-over toward revascularization during the follow-up (34% in the COURAGE and 46% in the BARI-2D). More recently, the Fractional Flow Reserve (FFR) vs. Angiography for Multivessel Evaluation 2 study has been the first clinical trial for patients with stable angina comparing optimal medical therapy vs. medical therapy and optimal revascularization guided by FFR and using second-generation drug-eluting stents. The study was suspended early (after enrolling 50% of the planned patients with only 7 months of mean follow-up), for the manifest superiority of the invasive strategy as far as the composite primary end-point of death, myocardial infarction (MI) and urgent revascularization is concerned. On the other hand, this result was determined by the ‘softer’ component of the primary end-point (reduction of urgent revascularizations), whether there was no significant difference between the two strategies for the other two outcomes. These results could hardly be extended to the elderly population because, as shown in Table 1, patients included in the studies were not of ‘geriatric’ age. This selection bias is inappropriate and unjustified, also considering the TIME (Trial of Invasive vs. Medical therapy) study, in which 301 patients with angina and age more than 75 years (mean 80 years) were randomized to an invasive or conservative strategy: patient after revascularization had – at 1-year follow-up – an earlier and better symptoms control and a better quality of life, even though there were no benefits in terms of ‘hard’ end-points. After 4 years of follow-up, however, revascularized patients had also a better survival (76 vs. 46%; \( P < 0.027 \)). Currently ongoing is the International Study of Comparative Health Effectiveness with Medical and Invasive Approaches trial (ClinicalTrials.gov number NCT01471522), a randomized, international, multicenter study financed by National Institute of Health/National Heart, Lung & Blood Institute.

The purpose of this trial is to compare the occurrence of a composite end-point (cardiovascular deaths and MI) in patients with stable ischemic heart disease and evidenced by at least moderate ischemia (exercise stress test, echo-stress, scintiscan or MRI), who are randomized to a conservative strategy based on optimal medical treatment vs. an invasive strategy in which the medical treatment is immediately integrated with angiographic evaluation intended to lead to optimal revascularization (CABG or FFR-guided PCI with second-generation drug-eluting stents).

Considering the limitation of the previously published trials and awaiting for the results of this ongoing trial – hoping that elderly patients, more representative of the actual clinical practice, will be included – the decision as to which strategy, conservative or invasive with myocardial revascularization, to recommend for elderly patients with effort angina is very challenging, and can scarcely be based on the current guidelines, but it should rather be personalized through a process of multidimensional geriatric assessment.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

References


© 2018 Italian Federation of Cardiology. All rights reserved.


