

Managing angina in the elderly: the impact of comorbidities

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Abstract

Older patients with angina represent a patient group with many clinical challenges. Coronary artery disease is particularly common in older patients and the mortality associated with cardiovascular disease is high. Furthermore, diagnosis can be difficult and comorbidities are common. Unfortunately, evidence from clinical trials based on this group of patients is limited and current treatment guidelines do not fully address the needs of elderly patients. Several recent clinical trials have highlighted some of the main considerations one should make when treating comorbidities in elderly patients with coronary artery disease. Different treatment options in the pharmacological management of angina in this age group with comorbidities are also discussed in this review.

Keywords: elderly; coronary artery disease; angina; comorbidities

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Introduction

The prevalence of coronary artery disease (CAD) increases dramatically with age. CAD is the leading cause of death in the elderly with 84% of all CAD deaths occurring in those 65 years of age or older. In women 70–84 years old, the prevalence of angina pectoris is 19%, and it is 24.7% in those aged 85 years and older. In men aged 70 years and older, the prevalence of angina is 27.3% [1, 2]. The disease is more likely to be diffuse and severe. One should also be aware of the higher likelihood for comorbidities in elderly patients with angina. Therefore, managing angina in the elderly is an increasing challenge, and one that we cannot and must not avoid.

Comorbidities in elderly patients with angina

Elderly patients more frequently have coexisting cardiac disorders, many of which can independently cause angina or exacerbate angina due to underlying CAD [3, 4]. These, along with non-cardiac conditions that can trigger angina symptoms, should be investigated as part of the overall evaluation. Of particular relevance are renal disease, other atherothrombotic disease (e.g., peripheral arterial disease or cerebrovascular disease), diabetes mellitus and anemia. Cardiovascular (CV) risk and management of CV risk factors and comorbidities in older patients with angina are discussed in detail below. Table 1 summarizes the key features of the most frequently reported comorbidities in older CAD patients.

Hypertension [6,11]	<ul style="list-style-type: none"> Isolated systolic hypertension is the commonest form of hypertension in elderly. The risk for CV events increases markedly in older patients. Even very elderly patients (>80 years) benefit from antihypertensive treatment (HYVET).
Diabetes [13]	<ul style="list-style-type: none"> The prevalence of diabetes mellitus is higher in patients aged >65 years with NSTEMI-ACS than in those aged <65 years. Myocardial ischemia may be silent in presentation which poses further difficulties in both the diagnostic and therapeutic management of CAD.
Renal failure [30]	<ul style="list-style-type: none"> Shares many risk factors with CAD. Elderly patients in whom the two conditions co-exist tend to have worse overall clinical outcomes with a higher risk for ischemic and bleeding complications.
Atrial fibrillation [21]	<ul style="list-style-type: none"> Common condition in elderly patients. Of the individual components of the CHADS2 score, age ≥75 carries a worse prognosis for stroke and mortality over hypertension, diabetes, or heart failure.
Peripheral vascular disease [31]	<ul style="list-style-type: none"> Elderly patients with stable angina often have atherothrombotic disease present in other arterial beds and this increases their total cardiovascular risk.
Aortic valve stenosis [20]	<ul style="list-style-type: none"> Angina is the most common symptom associated with aortic stenosis in elderly patients. CAD is frequently co-exists in these patients, however, angina may also occur in the absence of CAD.
Aortic incompetence [20]	<ul style="list-style-type: none"> Exertional angina may be present in patients with severe aortic regurgitation.
Mitral stenosis [20]	<ul style="list-style-type: none"> In patients without CAD, myocardial ischemia may be related to right ventricular hypertrophy or embolism.
Primary pulmonary hypertension	<ul style="list-style-type: none"> Chest pain is a non-specific symptom in patients with primary pulmonary hypertension. New onset of increasing severity/frequency of angina episodes can be a sign of deteriorating right ventricular function.
Anemia [27]	<ul style="list-style-type: none"> Mild to moderate anemia is a highly prevalent condition and an independent predictor of long-term outcome among elderly patients with stable symptomatic CAD.
Chronic obstructive disease [32]	<ul style="list-style-type: none"> This condition has common symptoms with CAD, triggered by exertion. Noninvasive assessment of CAD in COPD is difficult.
Hyperthyroidism [33]	<ul style="list-style-type: none"> Thyrotoxicosis can aggravate pre-existing heart disease and can also lead to AF, congestive heart failure, or worsening of angina pectoris.

Table 1 Comorbidities that frequently coexist in elderly patients with angina. AF atrial fibrillation, CAD coronary artery disease, COPD chronic obstructive pulmonary disease, HYVET Hypertension in the Very Elderly Trial, NSTEMI-ACS non-ST-segment elevation acute coronary syndrome.

Clinical assessment

The assessment of angina in the elderly can be difficult because pain caused by comorbid conditions (gastro-intestinal, musculoskeletal and pulmonary pain) can mimic angina pectoris. In addition, although angina usually indicates the presence of underlying obstructive CAD, myocardial ischemia can result from a variety of conditions that lead to an imbalance between oxygen supply and demand, such as left ventricular hypertrophy, aortic valve stenosis, atrial fibrillation with rapid ventricular response and chronic obstructive pulmonary disease. Of particular importance is that reduced activity levels and blunted appreciation of ischemic symptoms become the norm with advancing age. Therefore, angina in the elderly is neither a reliable nor a sensitive marker of myocardial ischemia.

Careful physical examination can reveal coexisting conditions that mimic or deteriorate angina symptoms (e.g., ejection systolic murmur in aortic stenosis), as well as comorbidities associated with a worse prognosis (e.g., bruits in carotid and femoral arteries).

Non-invasive tests

The 12-lead echocardiogram (ECG) is abnormal in over half of older people and may identify previous silent infarction or atrial fibrillation. It also provides important information about non-CAD disorders that may provoke angina symptoms, such as left ventricular hypertrophy or arrhythmias with slow or rapid ventricular response.

Exercise stress testing remains important in the elderly. However, the interpretation of exercise test

results in the elderly differs from that in the young. False positive test results are more frequent because of the higher prevalence of confounders, such as left ventricular hypertrophy (resulting from valvular diseases and hypertension), and conduction disturbances. Despite these differences, ECG testing should remain the initial test in evaluating elderly patients with angina and co-morbidities unless the patient cannot exercise; in such a case it may be replaced by pharmacological stress imaging.

If there are indications of valvular heart disease, left ventricular dysfunction, or left ventricular hypertrophy, an echocardiogram is essential. The presence of aortic aneurysm may be indicated by a detailed medical history and careful physical examination of the abdomen, and should be further investigated with ultrasound or computed tomography (CT) scanning. Similarly, carotid bruits should be evaluated using ultrasonic testing. Routine blood tests should be performed to assess hematocrit level, renal and thyroid function, lipid status and blood glucose. Finally, pulmonary function tests for older chronic smokers with chest pain and dyspnea on exertion adds to the diagnosis and management in elderly.

Management of elderly with angina and comorbidities

Angina

The presence or absence of comorbid conditions influences the selection of therapy in elderly. Preferred initial anti-anginal drug therapy is outlined in Table 2. Metabolic agents, such as trimetazidine or ranolazine, exert anti-ischemic actions without affecting hemodynamic parameters and thus represent useful adjunct

therapeutic agents in the elderly. The antianginal efficacy of I(f) inhibition with ivabradine is consistent across all the subpopulations analyzed, independent of the severity of angina and the presence of a comorbidity [5].

Hypertension

The targets for lowering blood pressure are the same for patients of all ages: less than 140/90 mmHg, except in patients with type-2 diabetes, chronic renal disease, established atherothrombotic disease, and heart failure, in whom a level of less than 130/80 mmHg is recommended [6,7]. No specific guidelines exist for hypertension management for this particular population. The choice of the first drug often needs to be precisely tailored to individual characteristics. Many patients will need two or more drugs to control blood pressure, since in the elderly it is often particularly difficult to lower systolic pressure to below 140 mmHg. Initial trial of a beta-blocker or a calcium channel blocker is justified as these agents exert anti-anginal effects in addition to lowering blood pressure. Caution should be exerted in identifying impulse and conduction disturbances when administering β -blockers or rate-reducing calcium channel blockers. Additional therapy with a diuretic or other anti-hypertensive agent should be used to adequately control the blood pressure [8]. Nonpharmacologic approaches (e.g., decreased sodium intake, weight reduction, exercise) also should be emphasized because they are more effective in older patients than in younger patients.

Isolated systolic hypertension (i.e., systolic blood pressure 140 mmHg or higher with a diastolic blood

Concomitant disease	Long-acting nitrates	β -blockers	Long acting DHP	Non-DHP	Ivabradine
Hypertension	+	+++	++	+++	++
Diabetes	+++	++	+++	+++	+++
Aortic valve stenosis	++	+++	+	++	++
SVT	+	+++	0	+++	+++
Chronic renal disease	+++	++	+++	+++	++
Peripheral vascular disease	++	++	+++	++	++
Mild COPD	+++	+	+++	+++	+++
Severe COPD	+++	0	+++	+++	+++

Table 2 Antianginal treatment options in older patients with comorbidities (modified from [34]). COPD chronic obstructive pulmonary disease, DHP dihydropyridine, PVD peripheral vascular disease, SVT supraventricular tachycardia. +++ very effective and desirable, ++ moderately effective and desirable; + effective but less desirable, 0 should be avoided.

pressure of less than 90 mmHg) is the most common form of hypertension in the elderly. A wide pulse pressure (i.e., 50 mmHg or higher) in this population is a better marker of cardiovascular risk than mean or diastolic blood pressure, emphasizing the dominant role of arterial stiffness in the pathophysiology of hypertension in the elderly [9, 10]. Trials specifically addressing treatment of isolated systolic hypertension have shown the benefit of thiazides and calcium antagonists, but sub-analyses of other trials also show efficacy of renin-angiotensin-aldosterone system (RAAS)-blocking agents [7]. Effects of blood pressure-lowering agents on central aortic pressure may differ despite similar effects on brachial blood pressure [11]. This finding provides a plausible explanation for increased benefit of agents, such as calcium channel blockers and RAAS-blocking agents, in the elderly. The Hypertension In the Very Elderly Trial (HYVET) was the largest-ever clinical trial to address the clinical uncertainty about the relative benefits and risks of antihypertensive treatment in patients over 80 years old [12]. HYVET showed that treating hypertension (with the aim to achieve a target blood pressure of 150/80 mmHg) with a regimen based on indapamide, with or without perindopril, is associated with reduced risks of death from stroke, death from any cause, and heart failure. The optimum diastolic blood pressure to be achieved by treatment is not clear; however, significant reduction in diastolic BP (<60 mmHg) should be avoided [7].

Diabetes

The recommended therapeutic interventions are similar across age groups and include dietary and exercise counseling, as well as pharmacologic therapies, with the goal of reducing the hemoglobin A1c level to less than 7% and achieving near-normal fasting blood glucose levels [13]. In elderly patients, lifestyle modifications leading to loss of body fat have a sizable positive impact on insulin and glucose metabolism. Exercise training improves insulin resistance and glucose control in healthy elderly persons [14]. In the ADVANCE trial, an intensive glucose control strategy involving glimepiride (modified release) and other glucose-lowering drugs as required reduced the hemoglobin A1c level to an average of 6.5%. The main benefit conferred by the ADVANCE treatment regimen was a 10% relative reduction in the combined outcome of major macrovascular and microvascular events, primarily as a

consequence of a 21% relative reduction in nephropathy [15]. It should be stressed, however, that every effort to avoid severe hypoglycemia should be made since it increases a broad range of adverse clinical outcomes.

Preventive management in older patients with diabetes requires critical attention to correcting coexisting cardiovascular risk factors. The addition of an angiotensin-converting enzyme inhibitor to other therapies slow the progression of kidney disease and reduces the risk for cardiovascular events in patients with diabetes and established CAD. However, clinicians should be aware of a higher risk of postural symptoms (e.g., orthostatic hypotension) in these patients.

Atherothrombotic disease

Secondary and primary prevention of ischemic stroke or transient ischemic attack (TIA) in older patients is targeted at modifiable risk factors including hypertension, active and passive smoking, hyperlipidemia and lack of physical activity. Prevention strategies are also targeted at high risk, but modifiable, conditions, such as inadequately treated atrial fibrillation and carotid artery disease [16, 17]. The benefit of LDL-c reduction on prevention of stroke is less clear in the elderly and no specific guidelines for aggressive lipid lowering strategies exist. The use of antiplatelet therapy is recommended for secondary prevention of atherothrombotic events in patients with prior stroke, TIA, or myocardial infarction. Anticoagulant therapy is recommended for patients with atrial fibrillation or patients who experience stroke while already on aspirin. Because older patients receive multiple antithrombotic agents much more often than their younger counterparts, initial steps toward optimized care include attention to indications, dosing, and duration of treatment [18]. Prasugrel therapy is associated with an increased bleeding risk. Prasugrel should not be used in adults older than 75 years of age and in those who have had a recent TIA or stroke [19]. Finally, patients with severe carotid lesions or symptomatic disease are candidates for carotid artery interventions.

Aortic valve stenosis

Aortic valve stenosis is a major cause of cardiovascular morbidity and mortality in older subjects. Furthermore, angina pectoris is the most common symptom associated with aortic stenosis in elderly patients.

Coexistent CAD is frequently present in these patients. However, angina pectoris may occur in the absence of CAD as a result of myocardial oxygen demand and supply imbalance at the subendocardial level. Once symptoms develop, aortic valve replacement should be performed in patients with severe or moderate aortic stenosis [20]. Nitrates and β -blockers should be used with caution for the symptomatic relief of patients with aortic stenosis in order to prevent the occurrence of hypotension and syncope. For the same reason, caution should be also exerted in the administration of diuretics in patients with heart failure.

Atrial fibrillation

Randomized controlled trials with Vitamin K antagonists (VKA) in atrial fibrillation have shown sustained reductions in ischaemic stroke and cardiovascular events, with only a slight increase in serious bleeds, resulting in a clear positive net effect of VKA in the elderly compared with aspirin [21].

β -blockers and non-dihydropyridine calcium channel antagonists are effective for rate control that may reduce the frequency of angina episodes in older CAD patients. Several randomized controlled trials have demonstrated that a strategy aimed at restoring and maintaining sinus rhythm neither improves survival nor does it reduce the risk of stroke in patients with atrial fibrillation. The AFFIRM study (Atrial Fibrillation Follow-up Investigation of Rhythm Management) in subjects aged 65 years or older (40 % had CAD) whose atrial fibrillation was likely to be recurrent and who were at risk for stroke reported an insignificant trend toward increased mortality in the rate control group, while there was no evidence to suggest that the rhythm-control strategy protected patients from stroke [21,22].

Patients at moderate to high thrombo-embolic risk require oral anticoagulation therapy. Recently, guidelines addressing antithrombotic therapy in such patients who also undergo coronary artery stenting were reported. These guidelines take into account the hemorrhagic risk, the clinical setting and the type of stent implanted [21,18,23]. A careful clinical evaluation and assessment of thrombotic/hemorrhagic risk before the beginning of anticoagulation therapy in elderly CAD patients with atrial fibrillation is essential.

An alternative approach aiming at reducing high severe bleeding rate involves combined antiplatelet

(cyclooxygenase inhibitor triflusal) and moderate-intensity anticoagulation therapy. In the NASPEAF trial, such a combination was effective in prevention of embolic events, while vascular events were significantly decreased [24].

Chronic renal failure

Chronic renal failure shares many risk factors with CAD. Control of glycemia is a priority in management of diabetic patients with impaired renal function. The target for lowering blood pressure is lower in hypertensive patients with chronic renal disease as compared to subjects with normal renal function (a level of less than 130/80 mmHg is recommended). Although no specific data to show superiority of RAAS-blocking agents for preservation of kidney function or prevention of cardiovascular end-points exist in elderly patients, it is anticipated that they indeed exert this preferential protective effect. A study in elderly patients with chronic kidney disease with a moderate decrease in GFR suggest that these drugs are tolerated and maintained in the long term as often as in patients without renal failure [4]. Dosage adjustments pose an additional treatment challenge. As many CV drugs are cleared through the kidneys, patients with renal dysfunction typically require lower doses [4]. Anticoagulant medication used in acute coronary syndromes such as enoxaparin and small molecule IIb-IIIa antagonists require a dose adjustment in the presence of renal impairment, irrespective of age [25]. Finally, age >75 years is an important predictor of contrast-induced nephropathy [26].

Anemia

Elderly patients are more likely to be anemic on initial presentation, posing a caution in the use of dual antiplatelet therapy (e.g., clopidogrel plus aspirin) and thus potentially limiting the use of percutaneous coronary intervention [27]. The challenge is to identify the best target Hb level for elderly patients with angina, taking into account any comorbid conditions (such as renal failure, gastrointestinal bleeding), concomitant medications and the patient's own expectations of therapy. In elderly patients with atherosclerosis, it is important to maintain Hb levels $10 > \text{g/dl}$ to prevent angina pectoris or congestive heart failure [27,28]. However, it remains unknown whether and how much anemia should be corrected in elderly CAD patients in order to improve outcome.

Chronic obstructive pulmonary disease

CAD is not rare in patients with chronic obstructive pulmonary disease (COPD) because both diseases share common risk factors, especially smoking, increased age and decreased physical activity. Non-invasive diagnosis of CAD may be under- or overestimated in patients with COPD. Furthermore, due to common risk factors and similar symptoms, coronary angiography may be performed more frequently in those patients. Nevertheless, specific treatments, such as beta-blockers, should not be denied to elderly people, unless specific contraindications are present, such as a severe chronic obstructive pulmonary disease or a history of asthma [29]. Wise adjustment of dosage should also be attempted.

Conclusions

Coronary artery disease is particularly common in older patients, but diagnosis of CAD can be difficult. Comorbidities such as renal disease, other atherothrombotic disease, diabetes mellitus and anemia are common. Unfortunately, specific clinical trial data to guide therapy in this growing population subset are limited. These patients can often be managed in the same way their younger counterparts, but additional care and considerations specific to the comorbidity is required. Given the increasing proportion of elderly patients in our aging societies and the increased CV mortality in these patients, further clinical research in this specific population is needed. •

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