Ischemic Heart Disease & Chronic Heart Failure in the Elderly

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Editorial

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I VECCHI TORNANO BAMBINI:
THE OLD RETURN TO CHILDHOOD

In a recent issue of Dialogues in Cardiovascular Medicine entitled “What If?” (2006, Volume 11, No. 1, pp 1-68), the editorial written by David and I recalled the now well-known, but nevertheless surprising fact that in the animal world there is a very clear relationship between the lifespan of mammals and their heart rate. That relationship, however, does not apply to humans. According to that relationship, human beings with a mean heart rate of 60 beats per minute should live no longer than 20 years. Fortunately, the majority of us enjoy a much longer life, and, in Western countries—but also increasingly in other parts of the world with emerging economies—our lifespan has gained 5 or 10 years over the last decade. This extended lifespan naturally reflects the success of medicine and improved social environment, but it also raises new questions, such as whether conditions like ischemic heart disease are exactly the same in the younger segment of the population as in the older one. The answer is clear: they are not.

We do not know precisely what happens to the heart during aging, but there is accumulating evidence that the aging heart differs from the adult heart and actually shares several close similarities with the neonatal heart. Strange isn’t it? We have a saying in Italy, “I vecchi tornano bambini,” which translates to “The old return to childhood,” (a far kinder and respectful way of saying that an elderly is in his/her dotage!). This is true, at least from a physiological and behavioral point of view, as the elderly often require just as much attention and care as a child. But, intriguingly this is also true of the aging heart, as many of the cellular components of the cardiomyocytes display the phenotype of embryonic life. This, of course, creates several problems, particularly regarding coronary artery disease where the so-called “compensatory mechanisms” for ischemic damage do not develop as easily.

There is no doubt that advanced age is a powerful predictor for ischemic heart disease. Ironically, although this is a very well known fact, the majority of clinical trials testing potential pharmacological regimens are conducted in young populations, leaving cardiologists with nearly no data to refer to regarding when to treat their “real-life”
elderly patients with coronary heart disease. Furthermore, compounding the above paradox, elderly patients are practically certain to exhibit comorbidities, which happen to be a clear exclusion criterion for the majority of clinical trials. Overall, this results in a completely distorted perception of the effect of drug treatments in the population that needs them the most.

This issue of Dialogues addresses this paradoxical situation by focusing precisely on the very few trials that specifically take into account the elderly population suffering from coronary artery disease.

In the Lead Article entitled “Ischemic heart disease in the older patient,” Steven P. Schulman, Edward G. Lakatta and Gary Gertenblith dwell on the distinctive features of coronary artery disease in the elderly, such as age as a powerful predictor of ischemic heart disease, increased comorbidity, atypical presentation of ischemic heart disease, decreased compensation, and increased bleeding risk following treatment. The authors conclude with three questions that introduce the Expert Answers section of Dialogues, which further specify these characteristics: “Is the presentation of acute coronary syndromes different in the elderly? (Michal Tendera and Wojciech Wojakowski); “Does cardiac remodeling after myocardial infarction differ in the elderly?” (Willem J. Remme); and “What is the best approach to lipid management in the elderly?” Lynne T. Braun. Their answers will give the reader a clearer picture of the implications of ischemic heart disease in the elderly patient and why longer life comes with several strings attached.
Advanced age is not only a powerful predictor for the development of ischemic heart disease (IHD), it also becomes, in established IHD, the most important risk factor for morbidity and mortality. The reasons lie in the increased comorbidity and frequently atypical presentation of IHD in the elderly, making diagnosis more challenging and often delaying the initiation of therapy. Age-related changes in the cardiovascular system compound the risk by making compensation more difficult once ischemic damage occurs. Even though many randomized controlled trials have enrolled relatively few older patients, the management of acute coronary syndromes in this population should still be informed by the resulting guidelines. Therapy in older patients with acute coronary syndrome has to be balanced against their known propensity to bleeding risk. Dose adjustments based on creatinine clearance can optimize benefit and decrease this risk. Given the increase in morbidity and mortality with acute coronary syndromes in the elderly, aggressive risk factor modification is vital for decreasing recurrent events. Appreciation of the benefits of such therapies in the older patient with IHD will hopefully decrease the high morbidity and mortality risk.

Advanced age is hugely relevant both to the development and consequences of ischemic heart disease (IHD), and to the treatment response. Over 85% of cardiovascular deaths occur in the elderly, along with most cases of congestive heart failure, atrial fibrillation, and hypertension. The consequences of IHD are also more severe, including fatal and nonfatal outcome, stable and unstable angina, and acute myocardial infarction (MI). Age is also commonly the most important determinant of the efficacy of aggressive therapeutic intervention, including angioplasty and bypass. The impact of advanced age on the development and consequences of IHD can be attributed in part to increased comorbidity, the severity and complexity of cardiac disease, and frequency of treatment complications. However, even after adjusting for such factors, there remains a significant and independent effect of age. The purpose of this article is to describe the known mechanisms of the age effect, estimate its magnitude in different ischemic settings, and review the management of IHD in the rapidly growing elderly population.

Studies of cardiovascular physiology in animal models and humans demonstrate several important changes in vascular and cardiac properties with age that increase the likelihood of atherosclerosis and decrease cardiovascular reserve. 

Keywords: acute coronary syndrome; aging; antiplatelet therapy; coronary artery risk factor; ischemic heart disease; lipid-lowering therapy; ST-segment–elevation myocardial infarction

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rosis, it also occurs in animal models in the absence of atherosclerosis. Endothelial dysfunction is one of the most important age-related changes in vascular properties and is believed to be involved in nearly every step in the development and manifestations of IHD.12,13 In men, the inflection point of change occurs at the beginning of the fifth decade, and for women in the seventh decade. Endothelial dysfunction is evidenced by a decreased response of the nonatherosclerotic brachial artery to endothelial-mediated induction of vasodilators. Increases in adhesion molecule expression and permeability to low-density lipoprotein (LDL) and macrophages are associated with smooth muscle cell migration and inappropriate vasoconstriction, resulting in rupture of the fibrous atherosclerotic cap. Endothelial function is believed to be largely dependent on the bioavailability of nitric oxide (NO), a coproduct of the conversion of L-arginine to citrulline catalyzed by endothelial NO synthase (eNOS).14 It is unlikely that a decrease in L-arginine availability is a contributing factor to decreased NO, since intracellular L-arginine levels are high and long-term supplementation is not associated with improved indices of vascular function or clinical events.15,16 However, eNOS activity decreases with age,17 and arginase I– and II–mediated conversion of L-arginine to urea and citrulline may decrease NO production in aged vessels. An increase in NO metabolism to peroxynitrite may also be associated with aging. There is an increase in arginase activity and peroxynitrite levels in animal models of vascular aging, and both are associated with mediators related to inflammation and oxidative stress.18,19

Primary and secondary IHD prevention has been mainly directed at decreasing factors that cause vascular injury (eg, hypertension, hyperlipidemia, smoking). However, it is becoming evident that it is equally important to address existing mechanisms that repair, regenerate and/or restore injured or damaged vascular cells. Mature endothelial cells from regions neighboring injured vascular tissue are known to participate in vasculogenesis. These replicative mechanisms are likely to be more limited in older vascular cells due to telomere shortening, decreased telomerase activity,
and oxidative damage.\textsuperscript{20,21} It is now recognized that new blood vessels are also formed by cells from distant sites, primarily bone marrow. There appears to be a significant age-related impairment in this ability, as demonstrated in studies in which angiogenesis following induced hindlimb ischemia was significantly diminished in an older animal model (\textit{Figure 1}).\textsuperscript{22} In addition, in murine models of accelerated atherosclerosis, transplantation of bone-marrow–derived cells from young, but not old, animals was associated with significantly decreased aortic atherosclerosis.\textsuperscript{23} Cells most closely associated with vascular repair are termed endothelial progenitor cells and are usually identified by the presence of both cluster of differentiation 34 (CD34) and vascular endothelial growth factor receptor–2 (VEGFR-2) markers.\textsuperscript{24} The number of these cells and their ability to give rise to colony-forming units are independent predictors of adverse outcome in patients with established IHD.\textsuperscript{25,26} In humans, age-related decreases in endothelial progenitor cell number and function have been described in patients undergoing coronary artery bypass graft (CABG) surgery.\textsuperscript{27,28} In one animal study, in which circulatory systems were shared between two animals, the pairing of an older with a younger animal restored the older animal’s progenitor cell count almost to the level of that in the younger animal.\textsuperscript{29} Thus, soluble factors from the young environment can reverse age-related progenitor cell changes present in the old environment.

In summary, important age-related vascular changes increase the likelihood of atherosclerotic disease and decrease the repair potential. Endothelial dysfunction is probably the most important factor contributing to the development of atherosclerosis. Although mechanisms are still being explored, increased inflammation and/or oxidative stress appear to be important underlying phenomena. In terms of repair, important age-related differences have been identified, but these do not appear related to intrinsic decreased progenitor cell number and/or function, and may be susceptible to modulation.

Age-related changes also limit cardiac muscle reserve following ischemic insult.\textsuperscript{1} Altered diastolic properties that increase early left ventricular end-diastolic pressure probably raise left atrial pressure. This is particularly evident during tachycardia but may also occur at normal heart rates, thereby increasing the risk of pulmonary edema, atrial arrhythmias, and congestive heart failure. The age-related changes include alterations in active state properties. Changes in myosin isoforms and sarcoplasmic reticulum function delay calcium removal from troponin and increase heterogeneity in the timing of relaxation. There are also changes in passive properties, including increased fibrosis. This delays early diastolic filling. Thus early left ventricular filling pressure has to be higher in the older individual to achieve the same stroke volume from the same end-diastolic volume.

One of the most important changes limiting cardiac muscle reserve is decreased \( \beta \)-adrenergic sympathetic responsiveness. This has been demonstrated in isolated trabeculae and whole heart animal models as well as in healthy subjects. It can be partly attributed...
to decreases in β1-receptors (in both absolute number and the proportion in the high affinity state), as well as to signaling changes distal to the receptor. These factors probably decrease the ability of noninfarcted myocardium to achieve the workload necessary to compensate for ischemic tissue damage. There are also age-related changes in the healing process that decrease the ability to form scar tissue resistant to infarct expansion and rupture. Important phenomena known to decrease ischemic injury are pre- and post-conditioning. In this paradigm, brief periods of ischemia before or after ischemic insult severely limit resultant damage. The mechanisms responsible are unclear, but the preconditioning effect is markedly attenuated or absent in older patients with IHD, while the postconditioning effect is lost in aging animal models.30-32

It is now recognized that heart muscle is not terminally differentiated. Very small numbers of endogenous cardiac progenitor cells can replace cardiomyocytes during an individual’s normal lifespan.31 These progenitor cells can self-renew or differentiate into smooth muscle, endothelial, or cardiac cells. They can improve cardiac performance when transplanted into syngeneic animals with infarction.33,34 Bone marrow cells also traffic to the heart and this phenomenon is significantly augmented in the presence of ischemic injury. It is probably a response to the release of proliferating and homing signals from injured tissue.35 Trafficking may be at least partly responsible for the gradual improvement in left ventricular function and shrinkage of infarct size that occur in the first postinfarction weeks. Nevertheless, this repair system is unable to restore normal structure and function after significant infarction, and is even less effective in most older individuals.36,37

The age-related decrease in repair potential may also be explained by the increased comorbidity associated with advanced age. For example, progenitor cells from patients with diabetes and congestive heart failure are less able to regenerate. Limits on progenitor cell number and function are also believed to be intrinsic to the aging process.37 The colony-forming activity of bone marrow–derived mesenchymal stem cells is decreased in animal models of aging and the replicative capacity of these cells is limited by similar mechanisms to those described above for endothelial cells.39 In aged mice, cardiac stem cell apoptosis is also increased.40 Administration of progenitor cells enhances myocardial function following infarction in animal models. The mechanisms responsible for this benefit are currently not clear. In addition to differentiation and cell fusion, secretion of paracrine factors from these cells enhances intrinsic progenitor cell migration, proliferation, and differentiation. Growth factors released from other sites also enhance these processes. Age-related decreases in several such growth factors, including platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), and estrogen, may also limit the production, homing, and function of progenitor cells.41,42 Additionally, older animals fail to respond to the exogenous cytokines (granulocyte colony-stimulating factor and stem cell factor) that improve endogenous repair processes in young animals.43

**RISK FACTORS FOR ISCHEMIC HEART DISEASE IN OLDER PATIENTS**

In general, the known cardiovascular risk factors originally identified in the Framingham and other observational studies apply equally in the elderly, except that their impact is more marked, while the effect on survival, although significant for most interventions, diminishes with age. In an elderly population, it is unrealistic to expect a long-term survival effect, meaning that it is especially important to focus on quality of life. This is not only significant for patients themselves, but also for their families and caregivers.

**Hypertension**

Hypertension is the most important reversible risk factor in the older population due to its prevalence and impact on mortality, IHD, and quality of life indices such as stroke and dementia. Prevalence exceeds 60% in the over-65s. The predominant presentation is isolated systolic hypertension caused by increased vascular stiffness. Analysis in over 1 million individuals reported a logarithmic increase in vascular events with increasing systolic blood pressure; it was steepest in the elderly.44 Two major trials have shown significant decreases in cardiovascular events with pharmacologic therapy in older individuals with isolated systolic hypertension. As first-line therapies the Systolic Hypertension in the Elderly Program (SHEP) used diuretics, and the Systolic Hypertension in Europe (Syst-Eur) trial a long-acting dihydropyridine calcium antagonist.45,46 They reported reductions in treated groups versus placebo of 27% in MI and coronary deaths, and 26% in cardiac events, respectively. Treatment was also associated with significant reductions in stroke and a 50% decrease in Alzheimer’s and non-Alzheimer’s dementia.47 A more recent larger study found no difference in primary cardiovascular end point when patients were randomized to a diuretic, angiotensin-converting enzyme (ACE) inhibitor, or long-acting calcium antago-
The selection of an agent is often dependent on comorbidity. A β-blocker is often recommended in the presence of active or recent ischemia, and an ACE inhibitor in ischemic left ventricular dysfunction (or angiotensin receptor blocker [ARB] if the ACE inhibitor is not tolerated). However, achieving the blood pressure goal using a cost-effective agent acceptable to the patient is more important than the particular agent used.

Hyperlipidemia

Hyperlipidemia is also common in the elderly. Although earlier studies did not adequately characterize its impact on coronary events, recent large studies have shown the benefit of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors for both the primary and secondary prevention of IHD. This topic is fully reviewed in Lynne Braun's article on lipid management and the elderly, in the present issue.

Smoking

Although smoking is less prevalent in the older population, it is associated with an increased risk for coronary events. Thus, the Established Populations for the Epidemiologic Studies of the Elderly (EPESE) project estimated the relative risk of cardiovascular death for current smokers versus never-smokers as 2.0. Smoking is also associated with other ischemic outcomes, including stroke and peripheral vascular disease. Smoking cessation is associated with significant clinical benefit, and those either side of 70 years enjoy a similar relative reduction in infarction risk. Thus it is important to emphasize to older individuals that by stopping smoking they can significantly reduce their stroke, MI, and other risks regardless of how long they smoked. Unfortunately, this is a difficult goal for most individuals. Success is best achieved with combined behavioral and pharmacologic approaches. Multiple attempts may be necessary. For the patient with known IHD, nicotine replacement products are not usually advised; the non-nicotine options of bupropion and varenicline are preferred. In randomized controlled short- and long-term trials, varenicline was associated with higher abstinence rates (40%-45% and 20%-25%, respectively).

Diabetes

The prevalence of diabetes and insulin resistance increases with age. Surveys conducted nearly 20 years ago estimated that over 13% of subjects aged ≥75 years had diabetes and another 14% had impaired glucose tolerance. These prevalences have probably risen higher since due to increases in sedentary lifestyles and obesity. The cardiovascular complications of diabetes, primarily IHD, are responsible for most deaths in this population. Although the cardiovascular benefits of tight glycemic control in patients with insulin resistance diabetes are not well defined, a hemoglobin A1c level below 7% is generally recommended. Most importantly, healthy lifestyle factors should be emphasized and blood pressure and lipid goals more vigorously pursued in this population.

DIAGNOSIS AND TREATMENT OF ISCHEMIC HEART DISEASE

Stable ischemic heart disease

Diagnosis

Despite the greater likelihood of IHD in the older population, symptoms may be less classic and evident. An older person is more likely to present with dyspnea than typical exertional chest pain. Indeed, symptoms of exertion may be less relevant due to activity limitations imposed by comorbidity. If IHD is suspected, stress testing may be confounded by preexisting ST-T-segment abnormalities, in which case imaging is useful, in particular stress echocardiography if the patient is echogenic. Testing may also be hindered by an inability to exercise to 90% of predicted maximum heart rate, in which case pharmacologic rather than exercise stress is employed, usually with dobutamine or dipyridamole (especially in patients on β-blockers). The sensitivity of such tests increases with age, up to 80% to 90%, but specificity declines, to about 70%. In addition, the likelihood of a false negative test increases in the elderly, while pharmacologic tests do not provide a functional estimate of IHD. Patients with a recent change in anginal pattern should also be investigated for potentially reversible factors, such as apathetic hyperthyroidism, new arrhythmias (particularly atrial fibrillation), anemia, and infection.

Pharmacologic therapy

A recent large randomized trial in stable angina patients with at least 70% coronary stenosis, documented ischemia, and anatomy suitable for angioplasty compared attempted optimal medical therapy alone versus optimal medical therapy plus percutaneous angioplasty. It found no differences in the primary end point of all-cause mortality and non-fatal MI over a median follow-up of 4.6 years. In the 904 patients older than 65 years, the primary end point event rates were 22% on medical therapy alone and 24% on medical therapy plus angioplasty.
The therapy used in this study defined current pharmacologic goals in stable angina and included aspirin, a long-acting β-blocker, dihydropyridine calcium channel blocker, and long-acting nitroglycerin alone or in combination, an HMG-CoA reductase inhibitor with an LDL goal of 60-85 mg/dL, a fibrate and/or niacin preparation with a high-density lipoprotein (HDL) goal of 40 mg/dL or higher, and a triglyceride goal of <150 mg/dL. The bleeding risk with aspirin increases with dose and age; increasing the dose from 75 to 325 mg/day provides no significant additional benefit, although it is not unreasonable to use up to 162 mg/day. Clopidogrel can be used in patients intolerant of aspirin.

Choice of β-blocker depends on comedication, concomitant renal or hepatic impairment (favoring hydrophilic and lipophilic agents, respectively), the requirement for relative β1 specificity in those with obstructive pulmonary disease, and half-life. Ophthalmic β-blockers are commonly used in the older population and may add to the effect of oral agents. For patients already on β-blocker therapy, a dihydropyridine calcium antagonist is preferred, while a nondihydropyridine is preferred in those not receiving a β-blocker. It is important to assess the blood pressure response, including orthostatic changes, whenever starting a patient on β-blocker or calcium antagonist, and when changing the dose. Long-acting nitrates can be tried, although intolerance is common. Trimetazidine, a metabolic agent with anti-ischemic properties due to inhibition of long-chain fatty acid oxidation, can improve angina when added to standard therapies. Creatine kinase is more common in the elderly. In patients with renal insufficiency, particular stress is on the proper use of sublingual nitroglycerin, particularly as a prophylactic before undertaking an activity likely to cause angina. It is important to warn of the dangers of combining nitroglycerin with a phosphodiesterase-5 inhibitor for the erectile dysfunction that is more common in the elderly. In patients with stable coronary disease, the addition of the ACE inhibitor perindopril to standard medical therapy reduces the 4-year risk of cardiovascular death, myocardial infarction, or cardiac arrest by 20% compared with matching placebo. This benefit was also notable in the 3831 subjects above the age of 65 years who were part of the study. Other important measures include lifestyle modifications, eg, weight loss if indicated, and exercise programs, which should initially be supervised.

**Revascularization**

An initial strategy of revascularization can be pursued in patients with suitable anatomy and without increased risk due to comorbidity. It should also be considered in patients who continue to experience ischemia despite medical therapy. In general, advanced age is associated with increased CABG mortality and morbidity, including stroke, dementia, and long-term disability. Thus although CABG may be associated with more complete and longer-lasting revascularization, percutaneous angioplasty or a hybrid approach, combining angioplasty with minimally invasive bypass surgery, should be considered if the anatomy is suitable.

Preexisting limited mobility may also influence the choice of therapies, since revascularization may not improve a physical activity status already compromised by other conditions, eg, arthritis or stroke.

Procedural success with percutaneous coronary intervention (PCI) is generally high (≥90%) in older patients with appropriate anatomy, and associated with a low complication rate. In stable angina, adverse outcome is most likely in patients with renal insufficiency, low ejection fraction, age over 85 years, inability to achieve complete revascularization, and coexisting diabetes. Recommendations regarding the short and longer-term use of dual antiplatelet therapy for patients with drug-eluting stents apply in equal measure to the elderly.

The increasing success of medical and catheter-based therapy for IHD has increased the number of older patients presenting for bypass and other surgical procedures. Although outcomes are generally worse without surgery in the elderly, predictors of early adverse outcome in stable patients include combined procedures (eg, valve and bypass surgery), advanced age, impaired left ventricular function, and comorbidity, particularly renal failure and pulmonary disease. Stroke risk is also increased in those with proximal aortic calcification and pre-existing cerebrovascular disease. Thus preoperative assessment should focus on pulmonary and renal function, cerebrovascular status, as well as the routine history, physical examination, chest x-ray, and laboratory tests. Postoperative care should include measures to decrease the likelihood of delirium, pneumonia, embolism, and bedsores.

**Acute coronary syndromes**

Clinical decision-making in elderly with an acute coronary syndrome (ACS) is complicated by the exclusion or under-representation of patients aged ≥75
years in many trials of relevant therapies or strategies. Mean population age in such trials has typically been several years below that of registry patients. Comorbidity such as chronic renal disease is also more common in ACS registries than in clinical trials.

This makes certain cardiovascular therapies and diagnostic tests more challenging in the elderly. A high clinical index of suspicion plus careful attention to the appropriate diagnostic tests and therapies are therefore especially important in assessing, diagnosing, and treating ACS in this population.

**Non-ST-segment–elevation acute coronary syndrome (NSTE-ACS)**

**Diagnosis**
The incidence of MI in the elderly has increased over the last 15 years, particularly in older women. NSTE-ACS is more often diagnosed in older than younger patients. Such older patients are more likely to be female and to have comorbidity such as angina, heart failure, hypertension, and diabetes. As in stable IHD, older ACS patients are more likely to present with atypical symptoms of acute myocardial ischemia and infarction, such as shortness of breath, confusion, and failure to thrive. Almost one-half of MI in the elderly goes clinically unrecognized. Such atypical presentations delay diagnosis and treatment initiation, thus helping to account for the elevated in-hospital mortality. A high index of suspicion for NSTE-ACS is mandatory in this age group.

**Prognosis**
Age is a powerful independent predictor of short- and long-term morbidity and mortality in NSTE-ACS. The Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin (eptifibatide) Therapy (PURSUIT) trial in 9461 patients with NSTE-ACS showed an increase in 6-month mortality from 2% in patients <50 years of age to 11% in those aged 70–79 years, and to 19% in those aged ≥80 years. Elderly patients with NSTE-ACS also have significantly higher incidences of cardiogenic shock and heart failure than their younger counterparts.

The high morbidity and mortality associated with ACS in the elderly dictate an aggressive approach to management. However, the evidence on which to base the care of elderly with NSTE-ACS is limited by the few patients above 75 years of age enrolled into clinical trials. Even ACS trials with no age restrictions usually exclude elderly patients with comorbidity, such as renal insufficiency or cerebrovascular disease. Thus, guidelines for treating elderly ACS patients are often based on limited information.

**Pharmacologic therapy**
Large registry cohorts show that most patients admitted with NSTE-ACS are aged ≥65 years. 38% are aged ≥75 years, and 11% ≥85 years. As age advances, recommendations about contraindicated treatments become more frequent, especially for glycoprotein IIb/IIIa antagonists. Nevertheless, even in patients without stated contraindications, in-hospital use of aspirin, β-blockers, and anticoagulation agents decreases with increasing age. Early invasive approaches to NSTE-ACS management are also reduced with advancing age, with only 40% of patients above 75 years of age proceeding to early catheterization. Decreased utilization of medications and procedures in elderly with ACS is mirrored by escalating in-hospital mortality, which is 2.5- and 3-fold higher in the 75–84 and ≥85 year age groups, respectively, than in under-65s. As guideline recommended therapies are used more commonly in-hospital and at discharge, the risk of in-hospital and short-term death is lowered in patients aged ≥75 years.

**Antiplatelet and antithrombotic therapy in non-ST-segment–elevation acute coronary syndrome**
In elderly patients with NSTE-ACS, antiplatelet therapy initiated on hospital admission decreases the number of events, while aspirin in daily doses from 75 mg to 1300 mg decreases short-term death and MI. In the Cooperative Cardiovascular Project (CCP) that reviewed over 10 000 MI patients aged ≥65 years, aspirin use reduced 30-day mortality by 22%. Aspirin therapy for NSTE-ACS appears as effective in preventing MI and death in elderly as in younger patients. Therefore, unless contraindicated, NSTE-ACS patients should receive nonenteric (rapidly absorbed) aspirin at doses from 162 mg to 325 mg as soon as possible after admission. After discharge, the daily dose should be reduced to between 75 mg and 162 mg to lower bleeding risk. In elderly patients treated with PCI and a bare metal stent, the aspirin dose should be lowered 1 month after stenting, and not for 3 to 6 months in those given a drug-eluting stent.

The thienopyridine derivative, clopidogrel, was evaluated in 12 562 patients with NSTE-ACS, all treated with aspirin. Treatment for a mean 9 months reduced the composite primary end point of cardiovascular mortality, nonfatal MI, or stroke by 20% versus placebo. This
benefit was also evident in the >65-year subgroup (n=6208). Thus in elderly patients with NSTE-ACS with low bleeding risk, clopidogrel added to aspirin for up to 1 year reduces future cardiovascular events. Chronic clopidogrel therapy is also indicated in elderly who are hypersensitive or intolerant to aspirin. Older patients in whom initially conservative management is indicated should receive a loading dose of clopidogrel 300 mg on admission followed by 75 mg daily. If the initial strategy is invasive, antiplatelet therapy in addition to aspirin is recommended prior to angiography. Current choices include clopidogrel, a glycoprotein IIb/IIIa inhibitor, or both. PCI outcomes are likely to be improved by a clopidogrel loading dose given at least 6 hours, and preferably at least 15 hours, before the procedure. Improved outcomes in elderly NSTE-ACS patients treated with clopidogrel prior to angiography must be weighed against the increased bleeding risk in the 10% to 11% of patients requiring CABG. A 5-day interval between a clopidogrel dose and surgery is recommended in order to reduce the bleeding risk.

Studies show that the addition of a parenteral glycoprotein IIb/IIIa inhibitor to standard anti-ischemic therapy including aspirin and heparin reduces short-term risks of death, MI, and refractory angina. The effect of a glycoprotein IIb/IIIa antagonist is consistent across age groups and is most beneficial in higher-risk patients, including those with positive troponin, ST-segment depression, and indications for coronary revascularization. In (positive troponin) patients undergoing PCI, the addition of a glycoprotein IIb/IIIa antagonist to aspirin, a loading dose of clopidogrel, and heparin reduces the 30-day rates of death, MI, and urgent infarct-related artery revascularization. Bleeding is more common with glycoprotein IIb/IIIa inhibitor therapy than with placebo, although there is no increase in the risk of cerebrovascular accident. Although it is important to monitor creatinine clearance prior to dosing in the elderly, due to the frequent need for dose adjustments, age should not exclude the addition of a glycoprotein IIb/IIIa inhibitor to standard anti-ischemic therapy for NSTE-ACS. This is particularly the case in higher-risk elderly proceeding to coronary revascularization.

Four anticoagulants recently studied in NSTE-ACS patients include unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), the direct thrombin inhibitor bivalirudin, and the factor Xa inhibitor, fondaparinux. The Superior Yield of the New strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa inhibitor (SYNERGY) study randomized 10 000 high-risk patients (NSTE-ACS plus age >60 years) due for coronary revascularization to UFH or the LMWH enoxaparin, in addition to standard aspirin and antiplatelet therapy. The primary end point of 30-day death or MI was similar in both groups. Bleeding risk was slightly higher in the enoxaparin group. The Fifth Organization to Assess Strategies for Ischemic Syndromes (OASIS 5) trial randomized over 20 000 NSTE-ACS patients, most managed medically, to enoxaparin or fondaparinux for 6 days. The primary end points of death, MI, or refractory ischemia at 9 days were similar in both groups. Results were also similar in a subgroup of approximately 12 000 subjects aged ≥65 years. Major bleeding was significantly lower in fondaparinux patients, significantly reducing the secondary end point of 30-day mortality. The Acute Catheterization and Urgent Intervention Trial Strategy (ACUITY) randomized nearly 14 000 NSTE-ACS patients, median age 63 years, to heparin plus glycoprotein IIb/IIIa inhibitor, the direct thrombin inhibitor bivalirudin plus glycoprotein IIb/IIIa inhibitor, or bivalirudin alone. In all patients the treatment goal was an invasive strategy. Patients treated with heparin plus glycoprotein IIb/IIIa inhibitor or bivalirudin alone had similar ischemic events at 30 days. The latter group had a significantly lower risk of major bleeding, suggesting that net clinical outcome was best with bivalirudin. Subgroup analyses indicated that patients treated with bivalirudin should also be treated with a thienopyridine to minimize ischemic risk.

The choice of anticoagulant for elderly patients with NSTE-ACS depends on bleeding risk and management strategy. In candidates for invasive therapy, enoxaparin, UFH, or bivalirudin appear appropriate. Patients treated with bivalirudin are unlikely to require routine glycoprotein IIb/IIIa inhibitor therapy, but should be given a thienopyridine. In those managed conservatively, enoxaparin or fondaparinux appear reasonable options, given their ease of use, especially the lower risk of bleeding with fondaparinux. Although antithrombotic and antiplatelet drugs reduce cardiovascular events in elderly patients with ACS, they must be used judiciously, due to the increased bleeding risk in this age group. Elderly with NSTE-ACS are often overdosed with anticoagulants and glycoprotein IIb/IIIa inhibitors, resulting in increased major bleeding risk, hospital stay, and in-hospital mortality. The most common cause of overdosing is failure to appreciate the dose adjustments required for antithrombotic agents, and several glycoprotein IIb/IIIa inhibitors, by the reduced creatinine clearance that is so common in elderly.
Invasive versus conservative strategy in non-ST-segment–elevation acute coronary syndrome

Several randomized trials have assessed the impact of conservative medical strategy versus an invasive approach on short-term outcomes of death, MI, and recurrent ischemic events in patients with NSTE-ACS. Most studies, particularly those performed in the coronary stent and antiplatelet therapy era, show a decrease in death or nonfatal MI for initial invasive strategy compared with conservative strategy. The benefit of an invasive approach was much more evident in higher-risk patients, including those with positive troponin, ST-segment depression on electrocardiography, and importantly, age >65 years. Analysis of randomized patients with NSTE-ACS showed large absolute and relative reductions in death or nonfatal MI at 6 months in subjects aged ≥65 years or ≥75 years using an invasive as opposed to a conservative approach.

These data suggest that an early invasive approach should be considered for many older patients with ACS. However, it should be noted that the randomized trials excluded a large percentage of patients due to contraindications, such as chronic renal disease or excess bleeding risk, that are common in the elderly.

ST-segment–elevation myocardial infarction

Prognosis

Age is also a powerful independent predictor of short and long-term morbidity and mortality in patients presenting with ST-segment–elevation MI (STEMI; Figure 2, page 14). In one study of patients admitted with a first STEMI and treated with thrombolytic therapy, in-hospital mortality increased exponentially with age from 1.9% in patients aged <40 years to 31.9% in those aged >80 years. In the Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded arteries (GUSTO-1) trial, 30-day mortality after STEMI increased from 3% in patients <65 years of age to 19.6% in those aged 75 to 85 years, and to 30.3% in those aged >85 years. Age was the most powerful predictor of hospital stay and 30-day mortality.

Elderly STEMI patients experience a much greater incidence of heart failure, atrial fibrillation, and cardiogenic shock even though indices of infarct size, such as creatinine phosphokinase levels and QRS scores, do not change with age. The risks of heart failure and cardiogenic shock increase 3-4 fold in patients...
Mortality in older patients with STEMI is less likely to result from ventricular fibrillation than in younger patients, but the elderly are much more likely to have electromechanical dissociation and cardiac rupture on autopsy. This risk is particularly notable in patients receiving fibrinolytic therapy. In elderly patients with STEMI, the high in-hospital mortality risk continues after discharge, increasing with age by almost 6% per year. Contributing to the increased risk in this age group is an age-related delay in reaching hospital for therapy. Elderly patients present with heart failure rather than chest pain, and with a much higher frequency of left bundle branch block, thereby complicating the electrocardiographic diagnosis of STEMI.

**Reperfusion in STEMI**

Most practitioners agree that prompt reperfusion of the infarct-related artery is critical in reducing the high mortality in elderly patients with acute STEMI. Unfortunately, the delays in reaching hospital and diagnosing acute STEMI, compounded by increased comorbidity, make elderly patients less eligible for reperfusion therapy. Large registry data in the US show that patients aged >75 years eligible for fibrinolysis are significantly less likely to receive reperfusion therapy than those aged <65 years. Data suggest that fibrinolytic therapy in acute MI reduces mortality in the elderly.

Subset analyses of the nearly 5800 patients aged >74 years in a meta-analysis of large randomized trials of fibrinolytic therapy showed a trend toward treatment benefit with a net saving of 1.0 life per 100 patients treated at 35 days after infarction. The benefit of fibrinolytic therapy was even more apparent over the age of 75 years when this meta-analysis was confined to patients presenting within 12 hours of symptom onset with ST-segment elevation or left bundle branch block on their admission electrocardiogram (34 lives saved per 1000 patients treated). It is difficult to draw conclusions as to the risk-benefit ratio of fibrinolytic therapy at ≥85 years of age, even in the absence of contraindications, as few such patients were enrolled into randomized trials. Currently, observational database studies show no benefit, or even harm, versus no treatment in patients aged ≥85 years. Part of the reluctance of physicians to use fibrinolytic agents in the elderly arises from the concerns about intracranial hemorrhage, for which age is a potent risk factor. Recent trials comparing half-dose fibrinolytic therapy plus a glycoprotein IIb/IIIa inhibitor versus full-dose fibrinolytic therapy have revealed the increased hemorrhagic risk of reperfusion strategies in the elderly, as have studies comparing fibrinolytic therapy plus LMWH versus UFH. Careful dose adjustment of the anticoagulant is needed to limit bleeding risk in the elderly. In considering fibrinolytic therapy in STEMI patients aged >75 years, mitigating factors include age, body weight, other comorbidity, the number of leads with ST-segment elevation, symptom duration, and the hospital's proximity to a high-volume center with onsite PCI. Recent data show that the benefit of fibrinolytic therapy is less at any time interval if pathologic Q-waves are present compared with those patients with only ST-segment elevation on the admission electrocardiogram.
Several trials versus fibrinolytic therapy have shown the benefits of primary PCI in terms of mortality, recurrent MI, and recurrent ischemia.\textsuperscript{119-121} Subgroup analyses indicate a large survival advantage for PCI over fibrinolytic therapy in patients aged \textgtr 70 years with STEMI.\textsuperscript{122} Primary PCI confers a lower overall thrombotic or hemorrhagic stroke risk compared to fibrinolysis.\textsuperscript{121} Patients with STEMI and a high-risk profile, including advanced age, derive greater benefit than low-risk patients from PCI compared to fibrinolytic therapy.\textsuperscript{123} One randomized trial of 87 patients aged >75 years with STEMI showed a significant decrease in death, reinfarction, and stroke at 30 days and 20 months after direct angioplasty compared to fibrinolytic therapy.\textsuperscript{124} An important caveat to all these comparative trials is that they involve operators with great expertise from high-volume angioplasty centers. PCI is preferable to fibrinolytic therapy if it can be performed expeditiously, generally with a door-to-balloon time under 90 minutes. However, the door-to-balloon time at which fibrinolysis becomes preferable to PCI in eligible elderly STEMI patients is debatable. In general, the target interval from the ability to open the infarct vessel with PCI compared with initiation of fibrinolytic therapy does not exceed 60 minutes. However, extensive observational data suggest that in STEMI patients aged \textgtr 65 years, this interval may be as long as 155 minutes. This longer window for performing PCI in STEMI probably reflects the increased risk of thrombolytic therapy in this age group.\textsuperscript{125}

Older patients are at higher risk of cardiogenic shock. Mean 6-year survival was significantly greater with early revascularization than with initial medical stabilization in one randomized study.\textsuperscript{126} Survival curves show that early revascularization confers an absolute long-term survival advantage of 13%. Since there is no interaction between treatment and age (<75 years vs \textgtr 75 years) over the long term, these data suggest that elderly acute MI patients with cardiogenic shock should receive urgent revascularization where possible.

**Medical therapy for STEMI**

\(\beta\)-Blocker therapy is greatly underprescribed in older post-MI patients, despite overwhelming evidence of a significant survival advantage. In the CCP database of over 200,000 Medicare beneficiaries with MI, only 34% of the elderly cohort was discharged home on a \(\beta\)-blocker.\textsuperscript{127} Of post-infarct patients above 65 years of age, with no contraindications to \(\beta\)-blocker therapy, only one half left hospital on this therapy. All age subgroups in this database had a large survival advantage (approximately 40% relative reduction and 10% absolute reduction in 2-year mortality) with \(\beta\)-blocker therapy.
confirming data from older randomized trials. The observed benefits extended to subjects with Q-wave and non-Q-wave infarction, age under 70 years to over 80 years, and all categories of left ventricular function. The benefits of chronic β-blocker therapy after MI in the database were similar to those revealed by subgroup analyses of the placebo-controlled trials of chronic β-blocker therapy following post-MI stabilization. Most of the long-term benefits of β-blockers in the large randomized trials were driven by the survival advantage in patients aged >65 years (Table II).128,129

Whereas long-term β-blocker therapy benefits all elderly patients after acute MI, aggressive intravenous then oral β-blocker therapy on hospital admission should be administered judiciously, if at all. In the Clopidogrel and Metoprolol Myocardial Infarction Trial (COMMIT), 45,852 patients with acute MI were randomized to intravenous then oral β-blockers or matching placebo.130 Those with cardiogenic shock, heart rate less than 50 beats per minute, or systolic blood pressure persistently below 100 mm Hg, were excluded. The proportion of patients free of reinfarction, cardiac arrest, or death in the first 28 days did not differ significantly in the β-blocker and placebo groups. Although early β-blockade reduced the incidence of reinfarction and ventricular fibrillation, this benefit was countered by a higher risk of cardiogenic shock on the first hospital day. Since age is a powerful predictor for the development of cardiogenic shock, elderly STEMI patients should be hemodynamically stable prior to β-blockade. In most instances, this can be done with oral therapy.

Aspirin decreases mortality and reinfarction in elderly infarct subjects.131,132 Nevertheless, among 10,000 Medicare beneficiaries with acute MI and no contraindication to aspirin, only 61% received aspirin in the first 2 hospital days.79 Although aspirin therapy in elderly infarct patients was independently associated with lower 30-day mortality and improved 6-month outcome, only 76% were discharged home on aspirin after MI.79 In a randomized, placebo-controlled trial of 45,852 medically treated patients with acute STEMI, clopidogrel plus aspirin reduced the short-term composite end point of death, reinfarction, or stroke as well as mortality alone.133 Subgroup analysis showed that all age groups benefited from this therapy. Dual antiplatelet therapy should therefore be considered in elderly infarct patients at low bleeding risk.

ACE-inhibitor therapy after acute MI reduces morbidity and mortality. The randomized placebo-controlled trials in high-risk patients with left ventricular dysfunction or clinical heart failure showed marked survival benefit in older patients randomized to ACE inhibitor therapy versus placebo.134-136 Meta-analysis of trials in 59,666 patients (mean age 63 years) with post-MI left ventricular dysfunction (ejection fraction <40%) or heart failure revealed a 26% reduction in mortality after a mean follow-up of 31 months in patients randomized to an ACE inhibitor137; secondary end points were also improved, including a 27% reduction in heart failure hospitalizations, and a 20% reduction in recurrent MI.137 Benefit was consistent across age groups (<55 years, 55-75 years, >75 years). ACE inhibitors are distinctly less beneficial in lower-risk elderly without heart failure or left ventricular dysfunction post-MI. Although clinical events do not appear reduced, the addition of an ACE inhibitor does decrease the progressive rise in left ventricular end-diastolic volume over the course of 1 year.138 Such patients require individualized treatment based on factors such as the risk of hypotension and renal insufficiency.139 Aggressive ACE inhibition on hospital admission should be avoided in the elderly as the resultant hypotension may cause ischemia and poorer outcome.

Older post-MI patients with left ventricular dysfunction, clinical heart failure, or both, failing to tolerate ACE inhibition (eg, cough) may be offered a high-doseARB as an equivalent alternative.140 The combination of ACE inhibitor and ARB adds no benefit over either agent alone and often causes greater side effects. In post-MI patients with left ventricular dysfunction, aldosterone production is stimulated, even with ACE-inhibitor therapy, and hepatic clearance is impaired.141 Elevated aldosterone levels may induce left ventricular fibrosis and progressive remodeling post-MI. In animal models of MI, aldosterone blockade prevents this progression.142 Randomized trials have shown that in post MI patients with both left ventricular dysfunction and heart failure, adding an aldosterone antagonist to standard post-MI therapy decreases cardiovascular morbidity and mortality, as much under as over the age of 65 years.143 An important caveat to adding an aldosterone antagonist to an ACE inhibitor or ARB in older post-MI patients is the frequent occurrence of renal insufficiency.144 Creatinine clearance should be calculated in this age group, and renal function and potassium levels closely monitored when using these agents.

Like β-blockers, aspirin, and ACE inhibitors, HMG-CoA reductase inhibitors (statins) reduce cardiovascular events in older post-MI patients and are similarly underprescribed. The Cholesterol and Recurrent Events (CARE) trial randomized 1283 post-MI patients (60%
Q wave) aged 65-75 years, with total cholesterol <240 mg/dL and LDL cholesterol 115-174 mg/dL, to pravastatin or placebo. Active therapy reduced 5-year cardiovascular event rates by a relative 32% and absolute 9% (19.7% vs 28 1%) versus placebo. Secondary end points (coronary death and stroke) were also significantly reduced. The numbers of older post-MI patients that needed to be treated with statin therapy to prevent one major cardiovascular event and one coronary death were 11 and 22, respectively.

The PRavastatin Or atorVastatin Evaluation and Infection Therapy (PROVE-IT) trial investigated more aggressive lipid-lowering therapy in a large cohort of ACS patients randomized to moderate lipid lowering with pravastatin 40 mg (mean achieved LDL 95 mg/dL) versus atorvastatin 80 mg (mean achieved LDL 62 mg/dL). Over the 2-year follow-up, the incidence of the primary end point of death, MI, stroke, revascularization, or readmission for ACS was significantly lower with aggressive therapy. Analysis showed similar benefit in patients aged ≥70 years.

Other large trials of secondary prevention have mirrored these impressive benefits of statin therapy in older post-MI patients. The Heart Protection Study (HPS) showed that the reduction in cardiovascular events after statin therapy for 5 years in its 5806 subjects aged ≥70 years, many with a history of MI, was as significant versus placebo as in the overall cohort. An observational study of 7000 patients with angiographic IHD (30% with MI) found significantly lower mortality after discharge on statin therapy, regardless of age, after 3.3 years of follow-up; however, prescription of statin therapy at discharge decreased significantly with age and was prescribed for fewer than one in five patients with IHD over 80 years of age. Although the few side effects of statin therapy are not age-related, only a minority of post-MI elderly leave hospital on statin therapy, and a large proportion stop statin therapy soon after discharge. Education of physicians and older patients in the benefit of risk factor modification after MI, including statin therapy, must continue to improve outcome in this high-risk group.

**Left ventricular remodeling**

Older STEMI patients are at higher short- and long-term risk of heart failure and left ventricular dilatation than their younger counterparts. Although the mechanisms involved are multifactorial, it is likely that age-related cardiovascular changes contribute. These include an increased arterial load, impaired β-adrenergic response, and impaired collateral blood vessel formation to the infarct zone. The elderly often present late with STEMI. To determine whether routine opening of an occluded infarct vessel late after MI onset prevents left ventricular remodeling and clinical events, the Occluded Artery Trial (OAT) randomized 2166 patients, with an ejection fraction <50% and/or angiographic proximal epicardial infarct vessel occlusion between 3 and 28 days after acute MI, to routine PCI with stent or medical treatment alone. The enrolment criteria required patients to be clinically stable, and free of heart failure and symptomatic ischemia. After 4 years, the primary end point of death, nonfatal reinfarction, or hospitalization for severe heart failure was 17.2% in the PCI group versus 15.6% in the medical group. In the 632 patients over 65 years of age, there was no reduction in clinical events for routine PCI, suggesting that older clinically stable patients arriving late with STEMI do not benefit from routine PCI of an occluded infarct vessel.

**CONCLUSION**

Most ACS patients are elderly. Advanced age is a powerful predictor of morbidity (primarily heart failure) and mortality in NSTE-ACS and STEMI. Although clinical trials often recruit younger patients with less comorbidity than seen in the community, large registry studies suggest that the application of guideline therapy to ACS patients saves lives. As major bleeding in hospitalized ACS patients is now recognized as a powerful predictor of future mortality, care must be taken to reduce this risk, in particularly in the elderly, in whom therapy may trigger bleeding. In elderly STEMI patients, consideration of fibrinolytic therapy versus PCI depends on a variety of factors, most importantly door-to-balloon time and the risk associated with fibrinolytic therapy. Hemodynamically unstable elderly have most to gain from a catheterization-based revascularization strategy. Hypotension is poorly tolerated in the elderly and care must be taken to avoid it. Future studies of ACS need to recruit more elderly and women to determine how to optimize care in these important and growing groups of patients.

Although there are many debatable management issues regarding IHD in older patients, the three most important questions are: how should ACS symptoms be diagnosed in older as distinct from younger patients? Does left ventricular remodeling differ in the elderly and, if so, should treatments differ from those in younger patients? And should cholesterol goals be the same or different in older patients with IHD compared to their younger counterparts?
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Ischemic Heart Disease &
Chronic Heart Failure in the Elderly

*Expert Answers to Three Key Questions*

1.
Is the presentation of acute coronary syndromes
different in the elderly?

*M. Tendera, W. Wojakowski*

2.
Does cardiac remodeling after
myocardial infarction differ in the elderly?

*Willem J. Remme*

3.
What is the best approach
to lipid management in the elderly?

*Lynne T. Braun*
Is the presentation of acute coronary syndromes different in the elderly?

Michal Tendera, MD, FESC, FACC; Wojciech Wojakowski, MD, FESC

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The heterogeneity of clinical presentation, response to treatment, and prognosis in elderly patients with acute coronary syndromes (ACS) is widely recognized. In patients >85 years, typical chest pain occurs in only 40% of cases compared with 77% in patients <65 years. Older patients more frequently complain of dyspnea, diaphoresis, nausea, vomiting, and syncope. ACS in older patients commonly presents as worsening heart failure (40% vs 20% in patients <65 years). The electrocardiogram on presentation is nondiagnostic in 23% of patients aged <65 years, increasing twofold in a subgroup of elderly patients aged >85 years. Diagnosis of ACS based on presenting symptoms can be more difficult because of a higher incidence of comorbid acute conditions that may mask the signs and symptoms of cardiac ischemia.

Keywords: acute coronary syndromes; elderly; symptoms; presentation; treatment

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SELECTED ABBREVIATIONS AND ACRONYMS

<table>
<thead>
<tr>
<th>Abbreviation</th>
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<tbody>
<tr>
<td>ACE</td>
<td>angiotensin-converting enzyme</td>
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<tr>
<td>ACOS (registry)</td>
<td>Acute CORonary Syndromes (registry)</td>
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<tr>
<td>ACS</td>
<td>acute coronary syndromes</td>
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<tr>
<td>CRUSADE</td>
<td>Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the American College of Cardiology/American Heart Association guidelines (quality improvement initiative)</td>
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<tr>
<td>ECG</td>
<td>electrocardiogram</td>
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<td>EMIP</td>
<td>European Myocardial Infarction Project</td>
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<td>GRACE</td>
<td>Global Registry of Acute Coronary Events</td>
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<tr>
<td>i*trACS</td>
<td>Internet Tracking Registry for Acute Coronary Syndromes</td>
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<tr>
<td>MI</td>
<td>myocardial infarction</td>
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<td>NRMI</td>
<td>National Registry of Myocardial Infarction</td>
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<td>NSTEMI</td>
<td>non-ST-segment–elevation myocardial infarction</td>
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<tr>
<td>PCI</td>
<td>percutaneous coronary intervention</td>
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<td>PRAIS-UK</td>
<td>Prospective Registry of Acute Ischaemic Syndromes in the UK</td>
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<td>ROSAI-2</td>
<td>Registro Osservazionale Angina Instabile–2</td>
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<td>SHOCK</td>
<td>SHould we emergently revascularize Occluded coronaries in Cardiogenic shock (trial)</td>
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<tr>
<td>STEMI</td>
<td>ST-segment–elevation myocardial infarction</td>
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<tr>
<td>VIGOUR</td>
<td>Virtual Coordinating Center for Global Collaborative Cardiovascular Research</td>
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ery” as individuals over the age of 75 years. Many clinical trials that serve as a source of evidence-based data that is subsequently used in the formulation of guidelines, actually exclude patients older than 75 years. In the trials that do enroll elderly patients with ACS, this population is underrepresented and comprises approximately 14% to 22% of the total number of patients, which is significantly less than that encountered in everyday clinical practice.1,2

The American Heart Association Council on Clinical Cardiology in collaboration with the Society of Geriatric Cardiology recently issued a scientific statement for healthcare professionals pinpointing the most significant differences in diagnosis, treatment, and outcomes in ACS patients of different ages (<65 years, 65-74 years, 75-84 years, and >85 years). Data presented in the statement come from more representative trials and registries (Virtual Coordinating Center for Global Collaborative Cardiovascular Research [VIGOUR], National Registry of Myocardial Infarction [NRMI], Global Registry of Acute Coronary Events [GRACE], 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), in which 31% to 40% of patients are older than 75 years.1,2

RISK FACTORS IN ACUTE CORONARY SYNDROMES

History taking as part of an initial risk assessment in ACS patients is a crucial part of the clinical evaluation. Data from the EuroHeart-ACS registry showed that the profile of risk factors was different in patients under 75 years, who more often presented with obesity, a familial history of coronary artery disease, and as someone who smoked, whereas patients over 75 years more frequently had a history of coronary heart disease, diabetes, and hypertension.3 Older patients with ACS are more frequently women.3,4 Other datasets (CRUSADE) have shown discordant results, suggesting that the prevalence of diabetes actually decreases in elderly patients over 85 years.5,6 Commonly used risk indices (based on such variables as age, heart rate, and blood pressure on admission) derived from randomized clinical trials in which elderly patients are not adequately represented, need validation, as they may have limited performance in this particular population (Table I).7 Growing evidence supports the finding that depression is a very common condition in the elderly, particularly those living alone. Moderate to severe depressive symptoms can lead to noncompliance with the treatment regimen as well as with cardiac rehabilitation.9

Furthermore, within the growing population of patients aged over 70 years, there may be differences in the risk profile and clinical presentation of the very elderly (>80 years) and the elderly aged 70 to 79 years. This stratification is important, because the 10-year age increment is associated with a doubling of mortality in ACS. Very elderly patients present significantly more frequently with heart failure, ST-segment–elevation myocardial infarction (STEMI), and renal failure, and less often have a history of revascularization. If coronary angiography is performed, octogenarians are more frequently found to have left main stenosis, but there are no other differences in the severity of coronary atherosclerosis (frequency of 2-vessel and 3-vessel disease) compared with patients aged 70 to 79 years.10 Data from an intravascular ultrasound study showed that octogenarians with myocardial infarction (MI) more often have long heavily-calcified plaques than patients younger than 65 years.11

SYMPTOMS AT PRESENTATION

The classic manifestation of myocardial ischemia in ACS is typical acute chest pain and discomfort (angina). Approximately 20% of patients presenting to the emergency department complaining of acute chest pain have ACS. Absence of typical anginal chest pain in patients with ACS can be associated

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Age &lt;65 years (%)</th>
<th>Age &gt;75 years (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family history of CAD</td>
<td>25-33</td>
<td>5-8</td>
</tr>
<tr>
<td>Smoking</td>
<td>26-52</td>
<td>3.3-9.0</td>
</tr>
<tr>
<td>Diabetes</td>
<td>23-28</td>
<td>33</td>
</tr>
<tr>
<td>Hypertension</td>
<td>35-41</td>
<td>64-69</td>
</tr>
<tr>
<td>Prior stroke</td>
<td>4</td>
<td>17</td>
</tr>
<tr>
<td>Renal failure</td>
<td>2</td>
<td>20</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>50-58</td>
<td>34-43</td>
</tr>
</tbody>
</table>

Table 1. Differences in pattern of risk factors in patients presenting with acute coronary syndromes according to age.3,4,6
with the misdiagnosis of MI, which can pose a serious threat—particular-ly in the setting of STEMI, which may also remain unrecognized—and this is because older patients tend not to attribute symptoms other than chest pain to the presence of coronary heart disease. In fact, MI remains unrecognized three times more frequently in patients over 85 years in comparison with younger subjects. A lack of typical symptoms may lead to the situation whereby the admitting physician does not consider ACS as a primary hypothesis in their diagnostic workup plan, which in turn results in treatment delay. This can adversely affect outcomes; indeed, the presence of atypical symptoms in elderly patients with ACS increases in-hospital mortality by a factor of three. Compared with patients aged under 85 years, there are a significantly higher proportion of patients aged over 85 years who present more than 6 hours after the onset of symptoms, and this difference is particularly evident in women, in whom it contributes to delayed initiation of appropriate treatment.

Data from the NRMI suggest that only approximately 50% of patients discharged with a diagnosis of MI were admitted with an initial diagnosis of infarction based on the symptoms reported in the emergency room. The NRMI found that in patients older than 85 years, typical chest pain was present in only 40% of cases, compared with 77% of cases in patients less than 65 years. With increasing patient age, there is a stepwise decrease in the frequency of presentation with typical chest pain, which is paralleled by a decrease in the diagnoses of ACS made following the initial evaluation of patients’ symptoms. The GRACE investigators reported that in older patients (mean age 72.9 years), the absence of typical chest pain was significantly more frequent than in younger individuals (mean age 65.8 years). On presentation, older patients much more frequently complained of dyspnea, diaphoresis, nausea, vomiting, and syncope (Table II). In general, the worsening of heart failure is a common manifestation of ACS in older patients. The NRMI also found that typical chest pain was present in 90% of patients presenting with STEMI who were younger than 65 years, and in 57% of patients older than 85 years. Stern et al carried out a multicenter survey aimed at assess-

<table>
<thead>
<tr>
<th>Symptoms/signs more frequent in patients &lt;75 years</th>
<th>Symptoms/signs more frequent in patients &gt;75 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical anginal chest pain (86%-90%)</td>
<td>Atypical pain/no pain (32%)</td>
</tr>
<tr>
<td>Dyspnea (40%)</td>
<td></td>
</tr>
<tr>
<td>Diaphoresis (26%)</td>
<td></td>
</tr>
<tr>
<td>Nausea and vomiting (24%)</td>
<td></td>
</tr>
<tr>
<td>Syncope (19%)</td>
<td></td>
</tr>
<tr>
<td>Weakness/fatigue</td>
<td></td>
</tr>
<tr>
<td>Heart rate &gt;100 beats per minute</td>
<td></td>
</tr>
<tr>
<td>Palpitations</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure &lt;90 mm Hg</td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td></td>
</tr>
</tbody>
</table>

Table II. Frequency of different signs and symptoms on presentation of older and younger patients with acute coronary syndromes.

In general, signs and symptoms of heart failure in ACS significantly increase in the elderly (from 20% in patients <65 years to 40% in elderly patients), as shown in several registries. In patients with STEMI, there was a significant increase in acute heart failure in the group of patients over 85 years (11.7% vs 44.6%). Data from the CRUSADE initiative comparing the clinical presentation of very elderly patients with acute MI (>90 years) and that of a younger subgroup (75-89 years) showed that the differences between these two patient age groups are less marked, with a higher number of nonagenarians presenting with heart failure, tachycardia, systolic blood pressure <90 mm Hg, and less frequently with ST-segment depression. These data, in concordance with those from other studies, indicate that major differences in the clinical presentation of ACS are more evident between groups of patients younger and older than 75 years.
INITIAL ELECTROCARDIOGRAM

According to guidelines, an electrocardiogram (ECG) should be obtained in every patient with chest pain within 10 minutes after presentation. Analysis of the data from the CRUSADE initiative showed a marked delay in obtaining the initial ECG in patients over 85 years compared with younger patients, and this delay was as long as 40 minutes in women older than 85 years. The initial ECG in elderly patients is significantly more often nondiagnostic than in younger patients, as shown by the NRMI: the frequency of nondiagnostic ECG on presentation was found to be 23% in patients younger than 65 years and increased twofold in a subgroup of elderly patients aged over 85 years.1,2

When analyzing the frequency of ST-segment changes present at admission, patients aged 75 years and above had more ST-segment depression and less ST-segment elevation in comparison with younger patients (42% vs 59% for ST-segment elevation; 28% vs 14% for ST-segment depression) (Table III). Consistently, data from the EuroHeart-ACS survey, which included more than 10,000 patients, showed a declining frequency of ST-segment elevation ACS in older men. In a subgroup of male patients aged less than 55 years, the incidence of ST-segment elevation ACS was 55% in comparison with 37% in a population of patients older than 85 years. There was also a significant increase in ACS with undetermined ECG pattern in older patients (increase from 1.7% to 16%).

In patients with STEMI, there was a decrease in the coexistence of typical chest pain and ST-segment elevation as patients’ age increased; the two were present in 72% of patients aged 75 years and above, compared with 90% of patients aged less than 65 years. Similar observations were made in a group of non-STEMI (NSTEMI) ACS patients, in whom typical chest pain and ST-segment depression were present in 83% of younger patients and less than 68% of older patients.4

The diagnosis of ACS based on the presenting symptoms can be more difficult in the elderly, because of a higher incidence of comorbid acute conditions (eg, pneumonia), which may mask the signs and symptoms of cardiac ischemia.

DELAY IN SEEKING MEDICAL CARE

A delay in the initiation of medical care in patients with ACS can worsen the outcome and contribute to the development of complications. Old age, female sex, and low socioeconomic status are among the major factors associated with a delay in seeking medical care.17

Increasing age has also been associated with more frequent use of the emergency ambulance service, however older patients have been found to have a significantly longer time lapse between the onset of symptoms and hospital admission (difference >1.5 hours between patients younger than 65 years and older than 75 years). This suggests that the elderly wait markedly longer before seeking medical care. This difference is particularly evident in patients with atypical chest pain or no anginal symptoms preceding ACS.4 Data from the international European Myocardial Infarction Project (EMIP) have shown...
Ischaemic Syndromes in the UK (PRAIS-UK), heparin and statins are used less frequently in elderly patients with ACS.\textsuperscript{21,22} Data from the CRUSADE initiative including 5557 patients aged 90 years and above, showed that contraindications to β-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, clopidogrel, glycoprotein IIb/IIIa inhibitors, and statins are significantly more frequent in this group of very elderly patients in comparison with younger patients (75-89 years), but also that these guideline-recommended medications are less frequently used—even in those without contraindications.\textsuperscript{6}

Despite the increased risk of drug-related adverse reactions, the benefits of guideline-recommended medications outweigh the risks. Elderly patients receiving intensive lipid-lowering therapy with statins to achieve a low density lipoprotein (LDL) level <70 mg/dL benefit from significant risk reduction of adverse cardiovascular events to an extent that is even greater than that in younger patients.\textsuperscript{23} Also, the benefits of treatment with a high dose of atorvastatin (80 mg) initiated 24 to 96 hours after presentation of ACS were similar for young and older patients, and the safety profile remained comparable with that of patients younger than 65 years.\textsuperscript{24}

Recent data support the implementation of an early invasive strategy in patients with ACS, especially in groups with elevated cardiac biomarkers levels and ST-segment changes. Due to a high rate of comorbidities, such as renal failure and generalized atherosclerosis, the elderly are often declined invasive treatment in fear of complications. The large Acute Coronary Syndromes (ACOS) registry has shown that among 1936 elderly patients (>75 years) with NSTEMI, the subgroup of younger patients with a lower risk profile is more often referred for early invasive treatment then those with a high risk, eg, cardiogenic shock, diabetes, or renal failure. This approach, however, leads to the exclusion of patients who might achieve a significantly higher risk reduction with an invasive approach. An invasive strategy is superior to medical therapy in terms of reduced in-hospital mortality (odds ratio [OR], 0.55; 95% confidence interval [CI], 0.35-0.86) and 1-year mortality (OR, 0.56; 95% CI, 0.38-0.81).\textsuperscript{15}

Elderly patients treated with percutaneous coronary intervention (PCI) are considered a high-risk group. Although patients older than 80 years more often have multivessel coronary artery disease, severe target vessel calcifications, smaller vessel diameter, and longer lesions, PCI can be performed safely with high procedural success rates (>97%) in this population. At the same time, however, the in-hospital and 1-year mortality rates increase, as well as vascular and bleeding complications.\textsuperscript{25}

In the prospective Registro Osservazionale Angina Instabile–2 (ROSAI-2), a registry of non-ST-segment elevation ACS carried out in Italy, early invasive strategy was used in only 39% of patients older than 75 years. The elderly were also less often referred for coronary angiography within 30 days post ACS. On the other hand, an early conservative strategy is an independent predictor of 30-day adverse events. The use of an early invasive strategy in the elderly should be encouraged, because this particular group of patients may benefit from an improved survival rate—in particular very old patients (>80 years).\textsuperscript{26} Older patients with ACS are more likely to be admitted to hospitals without a cath lab.\textsuperscript{27} Elderly patients also tend to be treated medically for acute MI. A study using data from the Pennsylvania Healthcare Cost Containment Council showed that patients treated medically are older and more often female than those treated with primary PCI. The survival benefit of PCI remained significant across all age groups, including in patients older than 85 years.\textsuperscript{28}

Furthermore, patients with cardiogenic shock, which constitute the group that has the highest mortality in ACS, are less frequently treated invasively. This is a particularly important issue, because as evidenced by the SHould we emergent-ly revascularize Occluded coronar-ies in Cardiogenic shock (SHOCK) trial, invasive treatment can significantly reduce mortality in elderly patients with cardiogenic shock (adjusted OR, 0.46; 95% CI, 0.28-0.75).\textsuperscript{29}

Despite evidence-based data, the attitude of the treating physician still strongly influences the use of treatment options recommended by the guidelines. In very elderly patients (>90 years), the age itself is often perceived as a contraindic-a-tion for invasive treatment involving PCI and the use of antithrombotic medications. Also, a lack of informed consent to undergo such procedures tends to be more likely in the very elderly (do-not-resusci-tate status). Access to specialized medical care may be different for very elderly patients. As shown by CRUSADE, this population of patients presenting with ACS is less likely to be treated by cardiologists, which can lead to underuse of more aggressive strategies.\textsuperscript{6}

The increasing evidence supporting the use of guideline-recommended treatment strategies may already have started to change the approach.
of physicians. Data from the Internet Tracking Registry for Acute Coronary Syndromes (**trACS) have shown that elderly patients are now more likely to be admitted to hospital after presenting to the emergency room with suspected ACS. There were also no differences found in the use of a stress test and cardiac catheterization between elderly and younger patients. 30

In addition, an analysis of temporal trends in the treatment of 20,550 patients aged 65 years and above who were admitted with acute MI revealed improved quality of care and increased survival over the period 1992 to 2001. At the same time, the mean age of patients increased from 75.7 years to 78.3 years, with a substantial number of patients aged over 85 years. Also, a higher proportion of patients were taking aspirin, β-blockers, statins, and ACE inhibitors before admission. Over the study period, the percentage of patients prescribed aspirin, β-blockers during hospitalization, as well as aspirin, ACE inhibitors, and β-blockers on discharge, increased substantially. The data show an encouraging trend toward more frequent use of guideline-recommended medications. However, since the profile of patients changed toward a population with a greater burden of comorbidities, the number of patients with contraindications for one or more of these medications also increased. Moreover, the mean length of hospitalization was reduced, and 6-month and 1-year survival rates improved in the elderly over the study period. 31

CONCLUSION
Advancing age is associated with a different clinical presentation of ACS, primarily because of a lower frequency of typical chest pain and a higher frequency of other symptoms, such as dyspnea, syncope, palpitations or absence of pain. In addition, the presence of both typical symptoms and ST-segment changes is less frequent in elderly patients with ACS. Clinicians should strongly consider ACS as a potential cause of such symptoms in the differential diagnosis in the emergency department. The difference in the clinical presentation encountered in old patients is an important issue, because it may lead to a delay in diagnosis, and treatment that could significantly improve the outcome.

REFERENCES


Does cardiac remodeling after myocardial infarction differ in the elderly?

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Sticares Cardiovascular Research Institute - Rhoon - THE NETHERLANDS

In the past two decades, heart failure (HF) has become one of the most important cardiovascular problems worldwide. It is characterized by fast-rising incidence and prevalence, high morbidity rates with frequent hospitalizations, and, above all, significantly shorter survival. Although underlying etiologies vary in different parts of the world, the major contributors are long-standing hypertension and ischemic heart disease, not only in the Western world, but also in developing countries. Both the prevalence and incidence of HF increase exponentially with age. The prevalence in the overall population is 2% to 2.5%; in octogenarians this increases >10-fold. Similarly, the incidence of HF in Western countries increases from 5/1000 inhabitants in the general population to 30 to 40/1000 in the over-75s. Two factors are recognized as major contributors to increasing HF prevalence. First, the improved treatment of acute coronary syndromes, includ-

The recent Perindopril and Remodeling in the Elderly with Acute Myocardial Infarction (PREAMI) trial was the first to study elderly patients (average age 73 years) with acute small myocardial infarcts (MI) and normal cardiac function. It showed that left ventricular (LV) volumes remained stable in the group treated with the angiotensin-converting enzyme inhibitor perindopril. Several small studies in the ischemic or post-MI setting show that cytokine and oxygen radical activation and apoptosis are all more pronounced in aging as compared to young hearts. Such mechanisms aid the remodeling process. Additional contributory factors in the aging heart include increased wall stress, LV hypertrophy, and myocardial stiffness. When combined with the PREAMI results, these observations suggest that post-MI remodeling is indeed different in the elderly.

Keywords: angiotensin-converting enzyme inhibition; heart failure; infarct size; left ventricular ejection fraction; myocardial infarction.

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Cardiac remodeling is a complex process in which the genomic and subsequently molecular, cellular, and interstitial responses to cardiac insult result in structural alterations, including an increase in chamber volumes, a more globular overall shape, and hypertrophy. While part of these changes may occur relatively fast, the entire process may take months to years to develop. Remodeling can follow different types of insult, including pressure or volume overload, inflammation, idiopathic cardiomyopathy, or MI. Different factors contribute to the process, either alone or, more often, in concert (Table I). They are often interconnected, eg, increased wall stress leads to neurohormonal activation (angiotensin II), which leads to cytokine activation, which leads to inducible nitric oxide synthase (NOS) activation, oxygen radical production, and apoptosis. The resulting molecular, structural, and functional changes include necrotic and apoptotic cell death, scar formation, hypertrophy, interstitial fibrosis, and collagen degradation. The ensuing macroscopic remodeling is associated with reduced contractility and relaxation, which can lead to progressive systolic and diastolic dysfunction and eventual HF.

### CARDIAC REMODELING AFTER MYOCARDIAL INFARCTION

Cardiac remodeling most commonly follows MI, but not every MI is followed by remodeling. The factors that determine whether, and to what extent, remodeling occurs include infarct site and size, previous infarcts, residual ischemia, persistent neurohormonal activation, continuously increased wall stress, and the effect of therapy.

Inflammatory response and cytokine activation are important contributors to remodeling early after MI. Cytokines such as tumor necrosis factor-α (TNFα), interleukin-1 (IL-1), and IL-6 are activated at this stage not only by ischemia per se, but also by mechanical deformation and wall stress in the infarct and peri-infarct area. Oxygen radicals are also important triggers of cytokine activation; perversely, these cytokines may then increase oxygen radical production by recruiting circulating inflammatory cells, thereby intensifying the remodeling process. In the acute phase, cytokines may lead to apoptotic cell death, but also to cell salvage (thus defining the net balance of cellular remodeling at this stage), and have direct negative inotropic effects. Chronically, cytokines have a regulatory role in collagen formation and degradation (by activating matrix metalloproteinas- es), scar formation, and further remodeling. They also upregulate angiotensin II type 1 receptors on cardiac fibroblasts, which may contribute to extracellular matrix remodeling and fibrosis.

As shown in animal models, the process of post-MI remodeling begins with cardiomyocyte lengthening, infarct expansion, thinning and dilatation of the infarct zone over one or more days, inflammation, necrotic tissue resorption, and scar formation. Subsequent stages include continued expansion of the infarct zone, myocyte loss, myocyte hypertrophy in noninfarcted areas away from the infarct zone, and reactive and reparative fibrosis of the interstitium. This may then lead to further cardiac dilatation and globular reshaping of the left ventricle (LV).

### HOW OFTEN DOES REMODELING FOLLOW MYOCARDIAL INFARCTION IN HUMANS?

It has been suggested that 24% of patients with a first uncomplicated infarct develop limited LV dilatation within 4 weeks, while dilatation and global LV dysfunction continue to develop in a further 20%. In contrast, in patients with early LV dysfunction after acute MI, 40% will develop LV dilatation and systolic dysfunction within 2 years.
CLINICAL SIGNIFICANCE OF CARDIAC REMODELING AFTER MYOCARDIAL INFARCTION

It has long been known that cardiac remodeling, in particular dilatation, is the harbinger of an unfavorable prognosis. This is also true for post-MI remodeling. LV volumes, in particular LV end-systolic volume, are significant predictors of survival in post-MI patients, along with the LV ejection fraction. In a Survival And Ventricular Enlargement (SAVE) substudy, angiotensin-converting enzyme (ACE) inhibition that failed to prevent cardiac dilatation over time in patients with LV dysfunction irrespective of ACE-inhibitor therapy. A well-performed study by Gaudron et al in 134 patients showed that the gradual increase in end-diastolic and end-systolic volumes after MI was significantly greater in nonsurvivors than survivors. Similarly, LV ejection fraction decreased progressively over time in nonsurvivors, but not in survivors (Figure 1). Interestingly, the authors also found a significant correlation between cardiac volumes and markers of arrhythmia, including the Lown criteria and QTc dispersion and duration. LV end-systolic volume remained a significant intermediate and late predictor of death and sudden death, respectively.

Similarly, the Gruppo Italiano per lo Studio della Streptochinasi nell’Infarto Miocardico–3 (GISSI-3) study in over 6000 patients with acute MI showed that predischarge echocardiographic end-diastolic and end-systolic LV lumen and ejection fraction values were predictive of 6-month mortality and heart failure. Patients with wall motion asynchrony <27% (ie, with intact cardiac function and smaller infarctions) had no LV dilatation.

CARDIAC REMODELING, NEUROHORMONAL ACTIVATION, AND THERAPY

Neurohormonal activation is a pivotal component of cardiac remodeling irrespective of cause. Neurohormonal antagonists are therefore essential in retarding or reversing the process. Prominent systems that activate remodeling include the sympathetic system, the renin-angiotensin system, aldosterone, and endothelins. The sympathetic

![Figure 1](image-url)

*Figure 1.* Continuous remodeling and baseline cardiac function determine prognosis. Left ventricular end-diastolic volume index progressively increases and left ventricular ejection fraction decreases over time in nonsurvivors, but not in survivors, after myocardial infarction.

systems (aldosterone included) became activated to a greater degree in cardiac tissue. Neurohormonal levels become markedly higher in tissue than systemically, and may be directly linked to (parts of) the remodeling process. For this reason, there have been studies with inhibitors of each system in the post-MI setting, but with different outcomes.

**Renin-angiotensin system**

Animal post-MI studies show significant increases in angiotensin II levels, persisting for at least 1 month after infarction.\(^{10}\) ACE activity increases or remains unchanged over this period.\(^{11}\) The effect on angiotensin II type 1 receptors varies, with both increases and decreases being reported, possibly dependent on the type of tissue being examined.\(^{1,11}\) In animal experiments, both ACE inhibitors and angiotensin receptor blockers (ARB) attenuated post-MI remodeling.\(^{12-17}\) In comparative studies, ACE inhibitors and ARBs had generally similar effects.\(^{12-14,17,18}\) although there is some evidence that ACE inhibitors may be superior.\(^{19,20}\) Combination therapy was usually better than either drug alone.\(^{14,21}\)

The greater effect of ACE inhibition could be explained by properties additional to those mediated by angiotensin I, eg, increased bradykinin production.\(^{19,22,23}\) In addition, although ACE inhibitors and ARBs may be similarly effective in containing myocardial hypertrophy, ACE inhibitors may be more potent in preventing non-myocyte cell proliferation and collagen deposition in noninfarcted myocardium.\(^{20}\) It is noteworthy in this regard that ACE inhibition attenuates the rise in cardiac cytokine expression for a prolonged period after infarction.\(^{24}\)

**Sympathetic system**

Sympathetic activation post-MI is caused by ischemic stress, additional neurohormonal activation, and myocardial stretch. Acute ischemia enhances catecholamine production, the resulting \(\beta_2\) - and \(\alpha_1\)-receptor activation then leads to increased heart rate, metabolic changes, arrhythmia, and vasoconstriction. Stretch, an early event in infarction, triggers \(\alpha\)-adrenergic activation and vasoconstriction. Unless treated, ischemia deepens, followed by cell death if cardiac catecholamine levels are high. The undisputed treatment in this setting is \(\beta\)-blockade, which has proved successful in managing post MI remodeling and survival. As both \(\beta\) and \(\alpha\) receptors are under siege, full adrenergic blockade with carvedilol is appropriate rather than selective \(\beta_1\) blockade alone. Moreover, carvedilol has additional antiapoptotic, anticytokine, and antioxidative properties that significantly boost its effect on remodeling in the post-MI patient. In the CArvedilol Post infarction survival ContRol in left ventricular dysfunction (CAPRICORN) study, carvedilol reversed ventricular remodeling versus placebo, and improved survival in patients with LV dysfunction post-MI.\(^{25,26}\)

**Aldosterone**

Aldosterone plays a pivotal role in cardiac disease. When overproduced, it may cause cardiac fibrosis and hypertrophy, endothelial dysfunction, reduced vascular compliance, and electrolyte disturbances. These may lead to hypertension, myocardial ischemia, arrhythmia, and HF. Although angiotensin II is an important stimulus, there are many others, and renin-angiotensin blockade alone does not suffice. Specific aldosterone (mineralocorticoid) receptor blockers such as spironolactone or the more selective antagonist eplerenone are mandatory in post-MI settings or HF.\(^{27,28}\)

After MI, cardiac aldosterone synthesis expression and aldosterone levels increase significantly, and mineralocorticoid receptors double. Eplerenone significantly reduced LV dilatation, LV collagen type I and II expression, and interstitial fibrosis in a rodent MI model, it also reduced ACE and endothelin-1 expression in noninfarcted myocardium. These effects were more pronounced when eplerenone was combined with an ACE inhibitor or ARB.\(^{29}\) Similarly, in patients with acute MI, spironolactone treatment for 1 month improved cardiac function, reduced LV volumes, and decreased plasma levels of procollagen type III amino-terminal peptide, a marker of fibrosis.\(^{30}\)

**POSTINFARCTION REMODELING AND THERAPY: WHAT THE LARGE TRIALS TELL US**

Current data on the long-term effect of therapy on cardiac remodeling post-MI in humans are derived mainly from ACE inhibitor studies. The only exception is CAPRICORN, which used the \(\alpha\) - and \(\beta\)-adrenergic blocker carvedilol.\(^{25}\) Although most ACE inhibitor studies were relatively small, they included five controlled studies in at least 100 patients over at least 6 months (Table II, page 40).\(^{7,31-34}\)

Although these studies varied in size, treatment duration, and timing of treatment initiation, they compare well with regard to patient age (mean 61 years) and degree of LV dysfunction (mean LV ejection fraction 43%). In placebo patients LV volumes increased throughout each study (6-12 months). The difference in the increase in LV end-diastolic
volume between placebo and active treatment was very small, approximately 1 mL in favor of the ACE inhibitor (NB, this excludes data from the SAVE study which measured dimensions rather than volumes). A recent meta-analysis of post-MI ACE inhibitor remodeling studies in patients with LV dysfunction revealed a slightly better effect (3.3 mL difference in LV end-diastolic volume in favor of ACE inhibition). However, these results should be interpreted with caution as the meta-analysis also included smaller placebo-controlled trials, in which there was significant heterogeneity. A fair conclusion based on the larger studies is that ACE inhibition may have a favorable, but small, effect on post-MI remodeling.

There are two common features to these post-MI remodeling studies. First, they were nearly always carried out in patients with LV dysfunction, and hence most likely large infarcts. Arguably, the effect of ACE inhibition on remodeling is likely to be greater in such patients than in those with small infarcts, intact function, and probably less neurohormonal activation. Second, the patients in these studies were relatively young, whereas the average age at which MI occurs in the general population is generally older. In men, a first MI occurs at an average age of 66 years and in women 70 years. Approximately 30% of MI occur in patients older than 75 years. This calls into question the relevance of the ACE-inhibitor effect observed in these studies to the general infarct population.

Unfortunately, in the elderly, there were few data on clinical end points post-MI and none at all on cardiac remodeling after acute MI—at least until the results of the Perindopril and Remodeling in the Elderly with Acute Myocardial Infarction (PREAMI) study were reported.

### THE PREAMI STUDY

The PREAMI study was designed to evaluate the effect of ACE inhibition on long-term cardiac remodeling and clinical end points, including death and hospitalization for HF, in elderly patients with acute MI but intact LV function. It was the first study of its kind in this patient population.

**Table II.** Controlled echocardiographic studies of post-infarction remodeling in populations exceeding 100 patients over at least 6-12 months.

<table>
<thead>
<tr>
<th>Study</th>
<th>Mean age (y)</th>
<th>Treatment</th>
<th>Patients (n)</th>
<th>Interval between MI and treatment start</th>
<th>Duration of follow-up</th>
<th>Mean LVEF at baseline (%)</th>
<th>Increase in LVEDV during follow-up (%)</th>
<th>Difference in LVEDV vs placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONSENSUS II</td>
<td>66</td>
<td>Enalapril 20</td>
<td>428</td>
<td>5 days</td>
<td>6 months</td>
<td>45</td>
<td>7.7</td>
<td>2 mL/m²</td>
</tr>
<tr>
<td>SAVE32</td>
<td>59</td>
<td>Captopril 150</td>
<td>512</td>
<td>11 days</td>
<td>2 years</td>
<td>31</td>
<td>2.0</td>
<td>3 cm²*</td>
</tr>
<tr>
<td>GISSI7</td>
<td>59</td>
<td>Lisinopril 10</td>
<td>6405</td>
<td>24 hours</td>
<td>6 months</td>
<td>47</td>
<td>1.4</td>
<td>0.7 mL</td>
</tr>
<tr>
<td>VALIANT33</td>
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<td>Captopril 150</td>
<td>204</td>
<td>5 days</td>
<td>20 months</td>
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<td>2.1</td>
<td>NA</td>
</tr>
<tr>
<td>CATS34</td>
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<td>Captopril 150</td>
<td>298</td>
<td>&lt;6 hours</td>
<td>6 months</td>
<td>56</td>
<td>10.2</td>
<td>0.8 mL</td>
</tr>
</tbody>
</table>

**Abbreviations:** AMI, acute myocardial infarction; CATS, Captopril And Thrombolysis Study; CONSENSUS, COoperative North Scandinavian Enalapril Survival Study; GISSI-3, Gruppo Italiano per lo Studio della Streptochinasi nell’Infarto Miocardico; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NA, not available; SAVE, Survival and Ventricular Enlargement; VALIANT, VALsartan In Acute myocardial Infarction Trial.

*Left ventricular end-diastolic cavity area; †VALIANT compared captopril, valsartan, and their combination, and was not placebo-controlled.
group. Over the 1 year follow-up, mean LV end-diastolic volume increased significantly by 4 mL. Volume was unchanged in the perindopril patients, resulting in an approximate 3.5 mL difference in the increase in LV volume between perindopril and placebo, in favor of the ACE inhibitor. This difference exceeded that shown in the larger post-MI studies with LV dysfunction (see above), and that observed in the one study with intact LV function (Captopril And Thrombolysis Study [CATS]). There was also a significant difference in the eccentricity index, with progressive reduction in placebo patients, but none in the perindopril group (Figure 2).

Thanks to the enhanced antiremodeling effect of perindopril (a highly significant reduction in relative risk of 46%), the primary end point in PREAMI (a composite of death, hospitalization for HF, and remodeling) was reduced by 38% in the perindopril group (P < 0.001). An additional prespecified analysis compared the incidence of cardiac remodeling, defined as an increase ≥8% in LV end-diastolic volume, between the placebo and perindopril groups. Significantly more placebo patients remodeled according to this definition than perindopril patients (51.1% vs 27.7%, P < 0.001, (Figure 3)).

Importantly, perindopril antiremodeling activity was consistent across all predefined subgroups, including age above/below the median, previous MI, hypertension, cardiac function at baseline, and background medication (eg, β-blockers and lipid-lowering drugs).

Although perindopril prevented remodeling, this did not translate into a difference in mortality or a significant reduction in hospitalization for HF (although it reduced this by 27%). This apparent discrepancy is fully explained by the short duration of the PREAMI study. Had it run for several years, it may well have revealed a difference in these clinical end points too. This conjecture is strongly supported by a retrospective analysis of the EUropean trial on Reduction Of cardiac events with Perindopril in patients with stable coronary Artery disease (EUROPA), which studied a similar population (post-MI, age >65 years, LV ejection fraction >40%) to that in PREAMI, using an identical dose of perindopril (8 mg), and a primary composite end point of cardiovascular death, nonfatal MI, and cardiac arrest. It suggests that perindopril would have significantly reduced the clinical end points in the PREAMI study had treatment been similarly continued for 4 years (Figure 4, page 42).

The PREAMI study prompts two interesting observations. The first is that cardiac remodeling occurs in elderly patients even in the presence of relatively small infarction and well-preserved ventricular function. Since studies in younger patients have ascribed post-MI remodeling to larger infarction, it is not surprising that remodeling was evident in elderly patients despite smaller infarcts. The second is that remodeling tends to be more severe in elderly patients than in younger patients, which is consistent with the concept that remodeling is an ongoing process rather than an acute phenomenon.

Figure 2. Changes in sphericity during treatment for 12 months in the Perindopril and Remodeling in the Elderly with Acute Myocardial Infarction (PREAMI) study. The eccentricity index decreased significantly in placebo patients, while remaining unaltered in perindopril patients. The significant intergroup difference indicates that the ventricle retained its normal ellipsoid form in perindopril patients.

Abbreviation: EI, eccentricity index.

Figure 3. Patients (% [95% confidence intervals, error bars]) with remodeling predefined as an increase ≥8% in left ventricular end-diastolic volume (LVEDV). Significantly more patients remodeled in the placebo group than in the perindopril group.

to LV dysfunction and presumably large infarcts, advanced age would appear to be a determinant factor in remodeling. The second is that ACE inhibition, at least with high-dose perindopril (8 mg/d), has marked antiremodeling activity in the elderly. This has not been shown in younger patients with intact LV function post-MI.

AGE-RELATED DIFFERENCES IN CARDIAC REMODELING AFTER MYOCARDIAL INFARCTION

In the PREAMI study, cardiac remodeling was more extensive than in younger patients undergoing comparable cardiac injury. Although speculative, this suggests that the remodeling process may differ between old and young hearts. The cardiovascular system undergoes many changes during aging, some of which may contribute to the accelerated and more pronounced remodeling seen in the elderly. The aging heart displays an increase in myocyte size, a decrease in myocyte number, and an increase in matrix connective tissue. Prolonged sarcolemmal calcium influx and reduced calcium sequestration by sarcoplasmic reticulum lead to sustained contraction and impaired relaxation. Contractile velocity is diminished by decreased β-receptor responsiveness and myosin adenosine triphosphatase activity. Myocardial stiffness increases and LV hypertrophy may ensue due to vascular hypertrophy and stiffening, ie, increased afterload. It is noteworthy in this regard that 58% of PREAMI patients had hypertension and that LV hypertrophy was more common in patients who remodeled than in those who did not (LV radius-wall thickness ratios: 1.84 vs 1.90; \( P=0.033 \)). As ventricular volumes tend to be smaller in the elderly, wall stress is likely to increase. Also, aging impairs endothelial function, possibly due to less nitric oxide (NO) production and more oxygen radical formation. In addition, apoptosis rates tend to be higher in older animals, at least in the post-MI setting. These cardiovascular changes predispose the elderly to myocardial ischemia due to imbalance between myocardial oxygen demand and supply, as well as to age-dependent endothelial dysfunction. Myocardial ischemia, oxygen radical formation, increased apoptosis rates, and increased wall stress are all pivotal factors in cardiac remodeling. They support the hypothesis, prompted by the PREAMI study, that post-MI remodeling indeed differs between elderly and young hearts in being more pronounced in elderly under comparable conditions.

The few data available from studies comparing cardiac remodeling in the post-MI setting directly between the old and the young support this
hypothesis. In acute ischemia-reperfusion studies, a much greater degree of cellular damage is observed in old compared to young murine hearts. In this setting, aging selectively modifies the ischemic responses of immediate early genes, and the genes involved in apoptosis and remodeling. Older rats show a higher cardiomyocyte apoptosis rate in the infarct border zone as well as in the noninfarcted myocardium.

Elderly patients (≥70 years) undergoing percutaneous angioplasty after a first anterior infarct had a greater increase in LV end-diastolic volume several weeks after the infarct and higher C reactive protein and IL-6 levels persisting for at least 6 months than patients aged <70 years, despite similar medication and angiographic findings. This study clearly points to augmented and prolonged inflammatory system activation after MI in older patients in association with more pronounced LV remodeling. Such studies support the notion that indeed aging per se is a determinant of cardiac remodeling.

ACE INHIBITION AND CARDIAC REMODELING IN THE ELDERLY

Although different neurohormonal antagonists may be of benefit in post-MI remodeling in the elderly, the currently available data suggest that inhibition of the renin-angiotensin system targets the problem at more levels than other agents (although the effect of aldosterone antagonists remains insufficienly characterized in this setting). Potential mechanisms include reduced peripheral and central pulse pressures, reduced ventricular wall stress, reduced adverse neurohormonal activation, and various anti-ischemic and antiapoptotic properties. Compared with other vasodilators, both ACE inhibitors and ARBs reverse cardiac remodeling in aging spontaneously hypertensive rats, partly by suppressing cardiac oxidative stress. Whether ACE inhibitors are more effective against post-MI remodeling than ARBs is uncertain. However, their effect on bradykinin production, and hence NO, may account for superior activity. But not all ACE inhibitors are equal in this respect. As Ceconi et al recently reported, they differ in their selectivity for the bradykinin binding sites of human somatic ACE: perindoprilat had the highest selectivity for bradykinin versus angiotensin I binding sites. A more recent study by the same group showed that perindopril had significantly greater effect on endothelial nitric oxide synthase (eNOS) protein expression and activation thantrandolapril, quinapril, ramipril, or enalapril at equihypotensive doses. Most importantly, perhaps, as far as post-MI remodeling is concerned, this group has reported significantly greater antiapoptotic activity by perindopril compared to other ACE inhibitors. Whether the PREAMI results can be extended to all ACE inhibitors is therefore uncertain and requires testing in comparative studies.

CONCLUSION

As shown in the PREAMI study, LV remodeling occurs in elderly patients after MI despite small infarct size, intact cardiac function, and optimized treatment, in contrast to the case in younger patients under equivalent conditions. In a setting of ischemia or postinfarction, elderly hearts appear more prone to pivotal factors in the remodeling process, such as cytokine activation, oxidative stress, and apoptosis. Advanced age per se would thus appear to be an important determinant of LV remodeling over and above infarct size.

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Cardiovascular disease is the leading cause of morbidity and mortality in the USA, and its prevalence increases with age. Hypercholesterolemia is a major cause of coronary heart disease, in particular in older adults. Clinical trials have shown that statin therapy decreases low-density lipoprotein cholesterol levels lowers cardiovascular events and mortality. There is evidence, albeit limited, that older subjects show benefit similar to that in younger subjects. Nevertheless, the use of medication must be approached judiciously in the elderly. Benefits should clearly outweigh the risk of adverse effects. Lifestyle changes (heart-healthy diet and regular aerobic exercise) remain the first-line of therapy for primary prevention in older adults. However, drug therapy should be considered in patients with multiple risk factors and in those with established coronary heart disease.

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in the United States. Its prevalence in Americans increases with age. Those aged ≥65 years have the highest incidence of new coronary heart disease (CHD) events, and account for 83% of related deaths.1 The United States Census Bureau estimates that there will be 40 million Americans aged ≥65 years in 2010. Population aging makes it especially important to detect and prevent CVD in the elderly. A major cause of CHD is hypercholesterolemia. This usually means an elevated level of low-density lipoprotein (LDL) cholesterol, since the LDL particle carries most of the cholesterol in circulation. Epidemiological studies show that CHD risk increases with the increase in LDL cholesterol, while clinical trials demonstrate that the use of statins to lower LDL reduces CVD events and mortality. For these reasons, the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults,2 known as Adult Treatment Panel III (ATP III), specified that LDL cholesterol is the primary target of lipid-lowering therapy.
therapy. By introducing substantial changes in CHD risk assessment and issuing prevention/treatment guidelines, ATP III expanded the population eligible for lipid-lowering treatment by a significant 131% among persons aged ≥65 years versus its predecessor ATP II (from 4 million to approximately 10 million older adults) (Table I).3

In patients without known CHD or other forms of atherosclerotic disease, ATP III recommends calculating a Framingham risk score to assess the 10-year risk of developing CHD. The purpose is to determine eligibility for more intensive LDL cholesterol management. Age has the greatest impact in the point values assigned to risk factors in the Framingham algorithm: from ages 65 through 79, point values range from 11 to 16, compared with lower point values assigned to the other risk factors. Since age is a nonmodifiable risk factor, it is imperative for therapeutic lifestyle changes to be implemented, along with drug therapies when necessary, to reduce modifiable risk factors.

Data from the Framingham Heart Study show that the cumulative risk of CHD rises steeply after age 60 years until age 90 years, when it tends to plateau. Even at age 70 years, the lifetime risk of a CHD event is 1 in 3 for men and 1 in 4 for women.4 Cumulative CHD risk in 70-year-old men is 42% in those with a total cholesterol ≥240 mg/dL vs 27% in those with a total cholesterol <200 mg/dL (the equivalent figures in women are 29% vs 14%).5 Thus higher cholesterol levels predict CHD risk even in older adults.

Patients with known CVD are at highest risk of CVD mortality and morbidity, and benefit most from lipid-lowering therapy and therapeutic lifestyle changes.2,6 Current guidelines recommend an LDL cholesterol goal of <100 mg/dL for high-risk patients. Those at even higher risk (established CVD plus multiple risk factors plus multiple major risk factors, including diabetes, smoking, and metabolic syndrome) have an optional LDL cholesterol goal of <70 mg/dL. Yet studies show suboptimal use of statins in the high-risk population.

The Cholesterol And Recurrent Events (CARE) trial6 included 1283 patients aged 65 to 75 years with myocardial infarction (MI), total cholesterol <6.2 mmol/L (240 mg/dL), and LDL cholesterol 3.0 to 4.5 mmol/L (115 to 174 mg/dL). As in 4S, pravastatin 40 mg/d in older patients reduced recurrent events by 32%, and CHD mortality by 45%.

### Table 1. Distribution of lipid-lowering treatment: eligible patients according to age.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>NCEP ATP II (n)</th>
<th>NCEP ATP III (n)</th>
<th>Increase in eligibility (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;45</td>
<td>3 866 019</td>
<td>11 650 593</td>
<td>201.4</td>
</tr>
<tr>
<td>≥65</td>
<td>4 200 419</td>
<td>9 706 158</td>
<td>131.1</td>
</tr>
<tr>
<td>60-69</td>
<td>3 615 222</td>
<td>7 775 595</td>
<td>115.1</td>
</tr>
<tr>
<td>70-79</td>
<td>2 401 312</td>
<td>5 525 541</td>
<td>130.1</td>
</tr>
</tbody>
</table>


20,536 men and women aged 40 to 80 years (including 10,697 patients aged ≥65 years) with CHD, other occlusive arterial disease, and/or diabetes. Subjects were randomized to simvastatin 40 mg/d or placebo for 5 years. Statin therapy significantly reduced all-cause mortality and the rate of a first major vascular event (coronary death, nonfatal MI, fatal and nonfatal stroke, and coronary and noncoronary revascularization). In particular, simvastatin significantly reduced the first major vascular event rate versus placebo, to 20.9% vs 27.2% in those aged ≥65 and <70 years, and to 23.6% vs 28.7% in those aged ≥70 years.

Type 2 diabetes mellitus (DM) is a potent risk factor for CVD. NCEP ATP III considers it a CHD risk equivalent. CARDS (Collaborative AtoRvasstatin Diabetes Study) was a 4-year double-blind randomized placebo-controlled trial of primary CVD prevention in 2838 patients with type 2 DM and an LDL cholesterol level ≤4.14 mmol/L, two thirds of whom were aged >60 years. Atorvastatin reduced the risk of major cardiovascular events by a highly significant 37% after a median follow-up of 3.9 years. Treatment also achieved noteworthy reductions in the risk of stroke (48%), acute coronary events (36%), and coronary revascularization (31%). Treatment would be expected to prevent at least 37 major vascular events per 1000 such people treated for 4 years. The investigators concluded that the use of statin therapy should be based on overall cardiovascular risk in all patients with type 2 DM rather than on a threshold level of LDL cholesterol as sole arbiter.

Clinical trial information on statin use in primary CHD prevention in the elderly is limited. The Airforce/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) examined the impact of primary prevention with lovastatin 20 to 40 mg/d on the incidence of a first major coronary event (fatal or nonfatal MI, unstable angina, or sudden cardiac death) in 2838 patients with a below-average level of high-density lipoprotein (HDL) cholesterol, 21.5% of whom were aged ≥65 years. The incidence was 6.8% in the lovastatin arm versus 10.9% in the placebo arm, namely, a reduction in relative risk of 37%.

Two recent studies exclusively in older patients showed that the benefits of statin therapy in hypercholesterolemia are similar to those in younger patients. The PROspective Study of Pravastatin in the Elderly at Risk (PROSPER) was the first randomized controlled trial to evaluate the effects of statin treatment specifically targeting the elderly. It compared pravastatin 40 mg/d and placebo in 5804 individuals aged 70 to 82 years. Participants had either preexisting coronary, cerebral, or peripheral vascular disease or cardiovascular risk factors such as smoking, hypertension, diabetes, and elevated total cholesterol. Statin therapy decreased mean total cholesterol by 34%. The incidence of the primary end point (CHD death, nonfatal MI, or fatal and nonfatal stroke) was 408 (14.1%) in the pra-
What is the best approach to lipid management in the elderly? - Braun

vastatin group versus 473 (16.2%) in the placebo group \(P=0.014\). For secondary end points (CHD death or nonfatal MI), the event rate was 10.1% in the pravastatin group versus 12.2% in the placebo group \(P=0.006\). When the patients were divided into primary versus secondary prevention subgroups, somewhat greater benefit was seen in the secondary prevention group, but the difference was not statistically significant.

The Study Assessing Goals in the Elderly (SAGE)\(^4\) compared intensive and moderate statin therapy (atorvastatin 80 mg/d vs pravastatin 40 mg/d) in 893 ambulatory CHD patients aged 65 to 85 years with at least one episode of myocardial ischemia on ambulatory monitoring. Although the groups did not differ in primary end point (ischemia duration on ambulatory monitoring) at 12 months, major CVD events tended to be fewer in atorvastatin-treated patients (hazard ratio, 0.71; 95% confidence interval [CI], 0.46, 1.09; \(P=0.114\)), with a significantly greater reduction in all-cause mortality (hazard ratio, 0.33; 95% CI, 0.13, 0.83; \(P=0.014\)). Thus SAGE demonstrated the benefit of intensive statin therapy in older subjects.

Elderly patients should be carefully evaluated for CVD risk factors, and therapies optimized accordingly. Treatment of modifiable risk factors can have a significant impact on outcomes in this population by increasing survival and improving quality of life. PROSPER showed a 15% relative risk reduction for CHD death, MI, or fatal or nonfatal stroke with pravastatin compared to placebo over a 3-year period. Yet lipid-lowering therapy remains underused in the elderly. A retrospective cohort study\(^5\) was conducted using health care administrative databases that included almost 400,000 Ontario residents aged \(\geq 66\) years with a history of CVD and/or diabetes. In this secondary prevention cohort of older patients, only 19.1% were prescribed statins, and the adjusted probability of statin prescription decreased as risk status increased. Furthermore, the likelihood of statin prescription decreased as age increased (Figure 1).

Although age should not be a factor in deciding who gets lipid-lowering therapy, medication use must be approached judiciously in the elderly. Obviously, the benefits should outweigh the risk of adverse effects. Nonpharmacologic interventions should be used whenever possible, and they remain highly recommend in conjunction with medication. When initiating medication in older persons, a low dose should be selected, and titration may need to be slower to achieve lipid goals.

Although clinical studies indicate no differences in safety and tolerability between lipid-lowering medications, the elderly are at increased risk for drug-drug interactions due to the use of multiple medications. Declining renal and hepatic function also impair their ability to metabolize and excrete medications. The elderly may be more susceptible to the specific myopathic effect of statins due to the relatively greater drug exposure of muscle tissue caused by the age-related decline in muscle mass. In addition, the incidence of hypothyroidism increases with age, which may also increase the risk of statin-induced myopathy.\(^6\) Thus the elderly require careful clinical and laboratory monitoring.

In summary, the decision to treat elevated cholesterol in an elderly person must be individualized with respect to overall health and co-morbidity. Advanced age carries the highest absolute CHD risk in the Framingham algorithm. Many such individuals categorized as requiring primary prevention have multiple CHD risk factors. ATP III increased the number of patients aged \(\geq 65\) years eligible for lipid-lowering therapy by 131% compared to previous guidelines. Subgroup analyses of secondary prevention studies have shown that statin therapy in the elderly is as effective in preventing CHD as in younger patients. Less information may be available in primary prevention, but it shows a risk reduction benefit in elderly persons. Therapeutic lifestyle changes (a heart-healthy diet and regular aerobic exercise) remain the first-line therapy for primary prevention in older adults, but medication should be considered in all patients with multiple CHD risk factors and in those with established CHD.

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Matters @ Heart

Dr John H. Gibbon and the first heart–lung machine

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History when presented as a mere recital of facts makes for difficult reading, but when connected to personalities, acquires flesh and blood. The term “past truth” refers to factual events accompanying a scientific discovery while “present poetry” stresses their human, romantic aspects.

The story of the development of cardiopulmonary bypass by Gibbon exemplifies the overall name of Past Truth and Present Poetry given to these articles first published in Heart News and Views (News Bulletin of the International Society for Heart Research), subsequently assembled in a book published in 2006 by TFM Publishing Ltd, and now republished in Dialogues and Cardiovascular Medicine. Cardiopulmonary bypass consists of temporarily replacing the heart and lung with artificial devices, permitting operation on a nonperfused heart in situ under direct vision. Gibbon’s contributions illustrate that discoveries can be made by minds whose scientific preparation is incomplete, but who achieve their goals by overriding motivation.

Dr John H. Gibbon was born in 1903, and almost did not become a doctor. During his college days at Princeton, he wanted to become a poet or a painter. But as he says, “My father pointed out like thousands of fathers before, that poetry is rather an uncertain mode of livelihood.” He writes that the first year in medical school was very boring. His interest in circulation started in his early medical days when he worked part-time with Dr Eugene M. Landis, who was a pioneer in the field of circulation. The idea for cardiopulmonary bypass originated from a clinical experience. In 1930 when he was a Surgical Research Fellow at Harvard, he was assigned to record the blood pressure and pulse every fifteen minutes of a female patient who had suffered a massive pulmonary embolus. Dr Gibbon continued through the night. Finally Dr Churchill, Head of Surgery, operated in a final effort to save the woman’s life. The operation, pulmonary embolectomy, carried a forbidding mortality. The embolus was removed, but the patient died. Gibbon wrote, “It was then that I found myself thinking how we could have helped her if we only had had some way of taking out the blue venous blood, getting oxygen into it while carbon dioxide escaped, and then putting the blood back into the arterial system.” This idea became his dream and his compulsion. He was fortunate to have as his wife and assistant the former Mary Hopkinson, daughter of the famous portrait painter Charles Hopkinson.
Gibbon found little encouragement. A Professor of Medicine at Harvard advised him against building an extracorporeal circulation. If he wanted to pursue an academic career in surgery, he should undertake a number of smaller and less ambitious projects that could be reported in the medical literature regardless of the results. Gibbon wrote that “The first heart–lung machine would have made Rube Goldberg envious.” It was built from improvised equipment such as a second-hand air pump, a collection of finger cots, and a box of rubber corks.

Gibbon had neither the skill nor the time for oxygen determinations. When in 1935 he succeeded in closing a cat’s pulmonary artery while maintaining the animal with a heart–lung machine, he wrote “I will never forget the day my wife and I threw our arms around each other and danced around the laboratory laughing and shouting hooray. Nothing in my life has duplicated the ecstasy and joy of the dance around the laboratory.” With no research grants he could not see his way to compete financially for the services of good engineers. Finally, he met Thomas J. Watson, founder and Chairman of the Board of IBM. Watson was encouraging. “You name the place and time and I will have engineers in there to discuss the matter with you.” In 1953, a patient from Wilkes-Barre, Pennsylvania, Cecilia Bavolek, consented to an operation. Cardiac catheterization had shown she had an atrial septal defect. For twenty-seven minutes during operation, all cardiorespiratory function was maintained solely by the machine.

Gibbon was emotionally drained following the historic operation. He did not personally dictate or write up the operation procedures because he did
not want relive the tension and emotional excitement by recalling the details. Gibbon retired at the age of sixty-four. As he wrote, "I entered college at fifteen, graduated from medical school at the age of twenty-three. I decided that since I started early, I could stop a little early." He died at the age of seventy-one while playing tennis.

There is no question that Dr Gibbon’s achievement represents a medical breakthrough comparable to the greatest discoveries in medicine. His achievement made possible open heart surgery, closing of septal defects, cardiac transplantation, operation on the valves of the heart, and last but not least coronary bypass surgery. The Nobel Committee usually awards the prize to scientists who have achieved breakthroughs in the field of basic science. With the probable exception of cardiac catheterization, the Committee has seldom honored technical advances. But Gibbon would have deserved this award. His work made modern cardiac surgery possible, saving thousands of lives.

**FURTHER READING**

Bing RJ, ed.  

Gibbon JH Jr.  

Gibbon JH Jr.  
Ischemic Heart Disease & Chronic Heart Failure in the Elderly

Summaries of Ten Seminal Papers

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1. Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises (Part I and II)

2. Aging is associated with endothelial dysfunction in healthy men years before the age-related decline in women
   D. S. Celermajer and others. J Am Coll Cardiol. 1994

3. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP)
   SHEP Cooperative Research Group. JAMA. 1991

4. Senescence and death of primitive cells and myocytes lead to premature cardiac aging and heart failure
   C. Chimenti and others. Circulation. 1994

5. Age-dependent impairment of angiogenesis
   A. Rivard and others. Circulation. 1999

6. Age and outcome with contemporary thrombolytic therapy. Results from the GUSTO-I trial
   H. D. White and others. Circulation. 1996

7. Age-related increase in mortality among patients with first myocardial infarctions treated with thrombolysis

8. Prognostic importance of physical examination for heart failure in non–ST-elevation acute coronary syndromes. The enduring value of Killip classification
   U. N. Khot and others. JAMA. 2003

9. Effect of beta-blockade on mortality among high-risk and low-risk patients after myocardial infarction

10. Coronary intervention for persistent occlusion after myocardial infarction

Selection of seminal papers by Steven P. Schulman, MD
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Highlights of the years by Ian Mudway, MD
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his outstanding review of cardiovascular aging argues that the powerful effect of increasing age on cardiovascular risk is based on the changes in cardiovascular structure and function with time that occur throughout the animal kingdom, altering the substrate on which disease mechanisms are superimposed. Risk in older subjects is increased because age-disease interaction not only makes disease expression more likely, but also makes the consequences of expressed disease more severe.

Lakatta and Levy discussed in cogent fashion the age-associated changes in the cardiovascular system that occur in healthy individuals who have no evidence of cardiovascular disease on extensive noninvasive testing. They drew on the healthy community volunteers enrolled in the Baltimore Longitudinal Study on Aging (BLSA), a well-phenotyped population that formed the basis for the following observations.

Arterial intima-media thickness increases 2-3 fold between the ages of 20 to 90 years in healthy individuals. Variation in this and other hallmarks of vascular aging in any specific age group makes the difference between successful and unsuccessful aging. The interaction of aging with disease becomes readily apparent when risk factors such as hypertension or hypercholesterolemia are added to this age-related finding of increased intimal thickness. Noninvasive measures of the arterial stiffness associated with intima-media thickening, such as pulse wave velocity, show a linear increase with increasing age, even in populations without atherosclerosis. As large conduit vessels stiffen with age, so systolic blood pressure increases, diastolic blood pressure falls (less elastic recoil by the stiff aorta in diastole), while pulse pressure, the difference between the two, rises linearly with increasing age in healthy populations. An elevated pulse pressure is recognized as a powerful predictor of cardiovascular events in healthy subjects as well as in patients with established cardiovascular disease. The vascular changes that occur with increasing age readily account for the epidemic of isolated systolic hypertension in the elderly.

In the BLSA cohort, echocardiographic wall thickness increased with age, presumably representing the heart’s response to the increased afterload that occurs with increasing age. Early left ventricular diastolic filling declined linearly with increasing age. The elderly therefore rely more on vigorou atrial contraction to ensure left ventricular filling. The response to exercise varies greatly in older compared to younger healthy individuals. Young subjects augment cardiac output by increasing heart rate and stroke volume, with a large decrease in end-systolic volume. Older subjects have an impaired β-adrenergic response, resulting in a blunted heart rate response and limited decrease (from rest) in end-systolic volume. Older subjects augment stroke volume with exercise via the Frank-Starling mechanism, giving an increase in end-diastolic volume. The BLSA studies of exercise after acute β-adrenergic blockade highlight the impaired catecholamine response to exercise with increasing age. The exercise hemodynamics of β-blocked young individuals resemble those of older subjects in that they rely on an increase in end-diastolic volume to boost cardiac output.

The increased arterial stiffness, decreased early left ventricular filling, and impaired β-adrenergic responsiveness in the elderly are fully compatible with health. However, the interaction of these age-associated changes with an additional disease burden, such as hypertension or coronary disease, accounts for the greater risk and severity of cardiovascular disease in the elderly.

Armed attackers kill 32 worshippers and wound a further 52, when they storm a Shia mosque in Quetta, Pakistan; comedian Bob Hope dies in his sleep, aged 100; and Ben Curtis becomes the first golfer to win a major golf tournament at the first attempt in more than 90 years.
Aging is associated with endothelial dysfunction in healthy men years before the age-related decline in women

D. S. Celermajer, K. E. Sorensen, D. J. Spiegelhalter, D. Georgakopoulos, J. Robinson, J. E. Deanfield

J Am Coll Cardiol. 1994;24:471-476

Endothelial dysfunction is recognized as a powerful predictor of cardiovascular events. One of the first signs of abnormal vascular function, presenting early in the pathophysiology of atherosclerosis, is the paradoxical vasoconstriction that occurs in response to a vasodilator stimulus such as acetylcholine or shear stress. First recognized in patients with established coronary disease, endothelial dysfunction was soon detected in those with minor coronary disease. Even those with no established disease, but simply with risk factors, were then shown to have paradoxical vasoconstriction of their brachial or coronary arteries in response to a vasodilator stimulus. Endothelial dysfunction results from a decrease in the endothelial release or activity of nitric oxide.

Taking a cohort of 103 healthy men and 135 healthy women of differing ages and with no risk factors for atherosclerotic heart disease, Celermajer et al used brachial artery ultrasound to show how the vasodilator response to shear stress (reactive hyperemia) becomes abnormal due to advanced age alone. In healthy men, brachial artery flow-mediated vasodilatation was preserved until the age of 40 years, after which there was a linear decline in endothelial function with increasing age. In women, flow-mediated vasodilatation was stable until the early 50s, after which it declined linearly. There was no age difference in response to the direct smooth muscle vasodilator, glyceryl trinitrate. Celermajer and coworkers were one of the first groups to demonstrate that endothelial dysfunction develops in healthy elderly subjects free of risk factors or vascular disease, suggesting that it occurs as a consistent feature of vascular aging, contributes to the increase in vascular stiffness, and increases the risk of cardiovascular disease in the setting of additional risk factors.

The mechanism of endothelial dysfunction in advancing age is multifactorial, but the end result is the impaired production or decreased biological activity of nitric oxide released from vascular endothelium. Appreciation of the mechanisms of endothelial dysfunction with aging may lead to novel therapies that decrease the risk of atherosclerosis in the elderly. The key reaction is the conversion of the substrate L-arginine by endothelial nitric oxide synthase to nitric oxide. In aging animal models, Berkowitz et al showed an increase in the activity and upregulation of arginase I, the enzyme that catalyzes the hydrolysis of L-arginine, thereby decreasing the substrate for nitric oxide synthase (Circulation. 2003;108:2000-2006, Circ Res. 2007;101:692-702). Inhibition of arginase I improved endothelial function and restored nitric oxide synthase activity in these models. The mechanism of increased arginase I activity involves an age-related increase in the vascular production of inducible nitric oxide synthase, ultimately resulting in nitrosylation of arginase and an increase in its activity. Such studies may eventually produce inhibitors of arginase activity, which safely improve endothelial function and perhaps decrease the risk of atherosclerosis.

Meanwhile, there is plenty of evidence to show that aggressive risk factor modification (aerobic exercise, weight loss, cholesterol lowering, and control of hypertension) enhances endothelial function. Therapies that may be uniquely beneficial in elderly patients include 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors and angiotensin-converting enzyme inhibitors, both of which have been shown to improve endothelial function.
Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP)

SHEP Cooperative Research Group

JAMA. 1991;265:3255-3264

Isolated systolic hypertension (ISH), caused by the increase in arterial stiffness with advancing age, is the predominant form of hypertension in the elderly, present according to national surveys in upwards of 70% to 80% of patients above 70 years of age. ISH is now recognized as a powerful predictor of cardiovascular morbidity and mortality in the elderly. Patients with ISH should be aggressively treated to a goal systolic blood pressure <140 mm Hg. However, not many years ago, ISH in the elderly was felt to be a natural part of the aging process, and one which it was best not to treat, for fear of lowering organ perfusion. It took the Systolic Hypertension in the Elderly Program (SHEP) trial to alert clinicians to the fact that not only is ISH in the elderly a potent predictor of events, but also that treating ISH with a diuretic-based regimen dramatically reduces events in this age group.

The SHEP trial, funded by the National Institutes of Health, was a 5-year double-blind randomized study in 4736 men and women aged ≥60 years with ISH that sought to determine whether a diuretic-based antihypertensive drug regimen reduces the primary end point of stroke. ISH was defined as a systolic blood pressure 160-219 mm Hg and diastolic blood pressure <90 mm Hg. The treatment goal, to reduce systolic blood pressure by ≥20 mm Hg from baseline and to <160 mm Hg, was achieved in 70% of the active treatment group compared to 35% of placebo patients. Average blood pressure was 12/4 mm Hg lower in the treated group than in the placebo group. Active treatment dramatically reduced 5-year stroke incidence to 5.2/100 vs 8.2/100, equivalent to a 36% reduction in total stroke risk. Benefit was evident across race and gender. Subsequent analyses showed that active treatment reduced the incidence of both hemorrhagic and ischemic strokes (JAMA. 2000;284:465-471). It also reduced the secondary end points of coronary heart disease by 25%, heart failure by 54%, and death by 13% (nonsignificant). In addition, in a further substudy (JAMA. 1998;279:778-780), it reduced echocardiographic left ventricular hypertrophy compared to an increase in left ventricular mass over 3 years in the placebo group. The drug regimen was well tolerated. Although there is concern about worsening metabolic parameters, such as glucose, potassium, and uric acid in older patients with hypertension treated with a thiazide regimen, serum chemistry changes in the SHEP trial were modest (Arch Intern Med. 1998;158:741-751).

The main message from SHEP, mirrored by the Framingham study, is that ISH is a powerful risk factor for stroke, heart failure, and coronary disease. The placebo group with untreated ISH had a very high 5-year event rate. The importance of the corollary, namely that treating ISH in the elderly reduces these risks, cannot be underestimated, especially since treatment targets can in most cases be achieved with an inexpensive, well-tolerated regimen.

Mount Pinatubo erupts in the Philippines; the body of former US President Zachary Taylor (1784-1850) is exhumed to establish whether he was assassinated by arsenic poisoning; and Croatia and Slovenia declare their independence from Yugoslavia.
many of us learned in medical school and accepted as fact that the adult heart is an end-organ incapable of self-regenerating. This dogma was overturned by Piero Anversa’s group (N Engl J Med. 2001;334:1750-1757) and others who showed that the human adult heart has a resident pool of cardiac stem cells capable of dividing and differentiating into myocytes, smooth muscle cells, and endothelial cells, and thereby participating in cardiac repair. In the Anversa paradigm shift, the heart is a self-renewing organ, with homeostasis being maintained by lifelong myocyte regeneration: senescent myocytes undergo apoptosis and are replaced by new myocytes derived from cardiac stem cells, in a cycle involving the entire cardiomyocyte population every 4.5 years (Circulation. 2006;113:1451-1463).

Maintenance of homeostasis by resident cardiac stem cells is not, however, necessarily synonymous with the ability to mount an endogenous repair response to myocardial injury, such as acute infarction. Experimental infarction studies have shown that stem cells also die. However, cardiac stem cells are frequently observed in the surviving myocardium, along with actively dividing myocyte precursors. Humans dying of acute myocardial infarction show an increase in cardiac stem cell numbers in viable myocardium. Although such an increase may limit left ventricular remodeling in viable areas, it confers no benefit in the infarct zone. Hence the explosion of small clinical trials to determine whether stem cells can be injected directly into or around the scar or down the infarct-related artery to decrease infarct size and improve left ventricular function (and ultimately prognosis).

Older patients are at greatest risk of adverse effects from myocardial injury. Anversa’s group investigated whether resident cardiac stem cells are also present in aged human hearts and whether they contribute to myocyte regeneration. In a classic series of experiments, they obtained myocardial biopsies from older patients with cardiomyopathy, a group of age-matched subjects with intact left ventricular function, and 10 young patients with idiopathic dilated cardiomyopathy. They identified senescent stem cells using markers of the telomere dysfunction that prevents stem cells from proliferating. Cardiac stem cells were present in the myocardial biopsies of all subjects: older patients with cardiomyopathy, older subjects without heart failure, and young subjects with dilated cardiomyopathy. The numbers of cells staining as cardiac stem cells per 100 mm$^2$ of myocardium were similar in both elderly hearts and young diseased hearts. Both were significantly higher than in older control hearts. Importantly, 60% of cardiac stem cells from old diseased hearts were senescent and unable to enter the cell cycle, compared to 14% in age-matched control biopsies, and 17% in young diseased biopsies. The senescent cells undergo apoptosis. Thus, cardiac stem cells are activated in both aged and young diseased hearts, except that in the former they are senescent and unable to participate in repair, undergoing apoptosis instead. This decreased regenerative capacity of the aged myocardium probably contributes to the increased frequency of heart failure in this population, in addition to the increased morbidity and mortality after injury such as myocardial infarction. Most of the basic science work examining the use of exogenous stem cells in cardiac repair has been in young animals. Whether stem cell therapy works in older patients with heart disease remains to be determined.

Senescence and death of primitive cells and myocytes lead to premature cardiac aging and heart failure


Circ Res. 2003;93:604-613

M. Pascal Couchepin becomes President of the Confederation in Switzerland; the Supreme Court of the United States allows the extension of copyright terms in the US; and the Canberra Bushfires occur in Canberra, Australia, killing 4 people
Age-dependent impairment of angiogenesis

A. Rivard, J. E. Fabre, M. Silver, D. Chen, T. Murohara, M. Kearney, M. Magner, T. Asahara, J. M. Isner

Circulation. 1999;99:111-120

It is now well established that age-dependent impairment of angiogenesis and vasculogenesis occurs throughout the animal kingdom. Angiogenesis denotes the production of new from preexisting blood vessels, while vasculogenesis is the process by which endothelial progenitor cells from the bone marrow home in on areas of injury or ischemia, then proliferate and organize into new blood vessels. In a study in 1934 patients with acute myocardial infarction and an occluded infarct vessel on angiography, Kurotobi et al (J Am Coll Cardiol. 2004;44:28-34) showed that there was an age-dependent decrease in the formation of collateral blood vessels to the infarct related artery. Lack of collateral blood vessels in the older patient cohort was independently associated with increased short-term mortality. Thus impaired collateral blood vessel formation may account in part for the increased mortality in older patients with acute myocardial infarction. This study provided clinical confirmation of the brilliant work in animal models of hind-limb ischemia.

In both a rabbit and murine model, hindlimb ischemia was produced by unilateral femoral artery resection in young and old animals. Measurements included hindlimb perfusion pressure, angiographic collateral formation, capillary density, ex vivo aortic endothelial nitric oxide production, and immunohistochemistry for vascular endothelial-derived growth factor (VEGF) messenger ribonucleic acid (mRNA) production and VEGF protein expression from ischemic muscles. In young mice, the ischemic hindlimb remained viable after femoral artery resection. In contrast, old mice had severe necrosis and autoamputation of the ischemic limb. Hindlimb perfusion pressure was reduced in aged versus young animals in both models. Angiographic collateral development in the ischemic hindlimb was absent in older animals, but substantial in young animals. Acetylcholine induced-vasodilatation of aortic strips was lower in old versus young animals, indicating age-associated endothelial dysfunction; consistent with this finding, nitric oxide production was also lower in older aortic strips. Expression of VEGF mRNA and VEGF protein was markedly reduced in ischemic tissues from older animals, while treatment with VEGF significantly improved collateral growth in older animals.

These important studies in two animal models showed that aging dramatically impairs the ability to form new collateral blood vessels to ischemic tissues. Subsequent studies showed that this age effect is caused by a decrease in both vasculogenesis and angiogenesis. Rivard et al interpreted their data as showing that the age-related failure to respond to ischemia is due primarily to endothelial dysfunction; aortic strips from old animals lose their ability to vasodilate in response to acetylcholine. Angiogenesis requires the proliferation and migration of endothelial cells, while vasculogenesis requires the mobilization and homing in to the site of ischemia of bone marrow endothelial progenitor cells. Because healthy endothelial cells are essential in each case, age-related endothelial dysfunction impairs both processes. This results in decreased nitric oxide production and decreased release of homing and growth factors, such as platelet-derived growth factor-B and VEGF, both of which are critical for collateral blood vessel growth.

The Denver Broncos win their second consecutive Super Bowl, defeating the Atlanta Falcons, 34-19; Britney Spears releases her debut album “Baby One More Time”; and an earthquake measuring 6.0 on the Richter scale hits western Colombia killing at least 1000
A study has contributed more to our understanding of the natural history of acute ST-segment–elevation myocardial infarction (STEMI) in the reperfusion era than the Global Utilization of Streptokinase and Tissue plasminogen activator (tPA) for Occluded coronary arteries (GUSTO-1) trial, which randomized over 41,000 patients with acute STEMI to several thrombolytic regimens within 6 hours of symptom onset. The large number of patients, absence of an upper age cutoff as an exclusion criterion, 30-day mortality end point, and recording of important demographic, historical, and therapeutic information provided new understanding of the natural history of STEMI. Given the increased frequency of elderly with STEMI, it is critically important to know how age relates to outcome in this growing subgroup in the reperfusion era.

Demographic data from GUSTO-1 confirmed that older STEMI patients are more often female and hypertensive than their younger counterparts; they also weigh less and are less likely to smoke. Prior symptomatic coronary artery disease was as common in patients <65 years as in those >85 years. At presentation, older patients had a higher Killip classification, presented later after symptom onset, and received later thrombolytic therapy. They were less likely to receive aspirin and β-blockers on admission with acute STEMI, or to undergo coronary angiography after thrombolytic therapy. Among those who did have a coronary angiogram, the proportion with triple vessel disease was substantially greater.

In-hospital events were substantially greater in older patients, and included total and hemorrhagic stroke, severe bleeding, cardiogenic shock, myocardial rupture, reinfarction, heart failure, hypotension, and atrial arrhythmia. Mortality at 1 day, 30 days, and 1 year rose exponentially with age. At 1 day and 30 days, it was more than 10-fold greater than in the youngest patients. After adjustment for all other known baseline clinical prognostic factors, age remained the strongest predictor of 30-day mortality. This landmark trial of thrombolytic therapy in a very large population confirmed that increasing age is the most powerful demographic predictor of short-term morbidity and mortality in STEMI patients. It leaves no doubt over the increased risk of heart failure, cardiogenic shock, and death in our older STEMI patients. The key to improving their outcome is to understand why their risk of morbidity and mortality is so high compared to younger patients. The many potential reasons include the higher frequency of severe coronary disease and prior myocardial damage shown in this study. GUSTO-1 and other studies have shown that older patients present with STEMI later than younger patients and are less likely to receive aggressive therapy, such as thrombolysis, β-blockade, aspirin, 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors, and cardiac catheterization with revascularization. Other contributory factors probably include age-associated changes in the cardiovascular system, which make older patients less able to mount an effective response to infarct injury.

N

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King Fahd of Saudi Arabia temporarily gives power to Crown Prince Abdullah, his legal successor, due to illness; serious fighting breaks out between Russian soldiers and rebel fighters in Chechnya; and Colonel Ibrahim Baré Maïnassara deposes the first democratically elected president of Niger, Mahamane Ousmane, in a military coup.
Few studies affected how practitioners view elderly infarct patients than this analysis by the Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto miocardico 2 (GISSI 2) investigators. Before this study, the increased risk of morbidity and mortality in older patients with ST-segment-elevation myocardial infarction (STEMI) was thought to lie in their greater likelihood of myocardial damage prior to the index infarct, resulting in higher risks of heart failure, cardiogenic shock, and death.

This analysis of in-hospital and 6-month mortality included STEMI patients eligible for thrombolytic therapy. For 9720 of the 12 381 patients, it was their first myocardial infarction. Demographics (including age), Killip class, electrocardiogram, and cardiac enzymes were evaluated as predictors of mortality. Postmortem data were available for 158 of the 772 patients who died in hospital.

Indices of infarct size, such as the number of electrocardiographic leads with ST-segment elevation, and peak creatinine kinase were similar in patients aged <60 years, 61-70 years, and >70 years. Killip class and evidence of left ventricular dysfunction were substantially greater in older patients despite similar infarct size in those with a first STEMI. Increased age was a powerful predictor of short-term mortality on multivariate analysis; other predictors included increased Killip class, anterior infarction, and a high number of leads with ST-segment elevation on the admission electrocardiogram. As a continuous variable, in-hospital mortality increased exponentially with age by 6% per year; in-hospital mortality was 31.9% in those aged >80 years versus 1.9% in those aged ≤40 years. Markers of infarct size, creatinine kinase, and the number of leads with ST-segment elevation were not age-related. The etiology of death tended to be electromechanical dissociation in older patients and ventricular fibrillation in younger patients. Cardiac rupture was found in 65% of postmortems; its incidence increased steeply with age. In addition, 6-month mortality in hospital survivors also rose steeply with increasing age, from 0.8% in patients aged ≤40 years to 11.6% in those aged >80 years.

This important study confirmed that even in older patients with a first myocardial infarction and healthy enough to be eligible for a trial of thrombolysis, short-term mortality rises exponentially with increasing age. We also learned from this large cohort that indices of infarct size do not differ between older and younger patients with a first STEMI, suggesting that the high risk in elderly infarct patients cannot be attributed to increased ischemic damage. Nevertheless, the elderly have high rates of advanced Killip class and myocardial rupture on autopsy. This paradox must therefore be explained by factors other than the infarct itself. The increased ventricular and vascular stiffness, decreased β-adrenergic response, decreased early diastolic filling, and impaired stem cell repair discussed in the other seminal papers probably contribute greatly to the increased risk in elderly infarct patients.
The Killip classification was initially described in 1967. In that landmark paper (Am J Cardiol. 1967;20:457-465), Killip recognized the importance of physical examination in the risk stratification of patients with a Q-wave myocardial infarction. He showed a stepwise increase in short-term mortality based on the physical examination findings. Killip I patients had no evidence of heart failure, Killip II patients had mild heart failure with rales involving one third or less of the lung fields, Killip III patients had pulmonary edema, and Killip IV patients had cardiogenic shock with rales and systolic blood pressure <90 mm Hg. The Killip class has retained its prognostic value in patients with ST-segment–elevation myocardial infarction (STEMI), even in the setting of thrombolytic therapy or percutaneous coronary intervention. In patients with non ST-segment–elevation acute coronary syndromes (NSTE-ACS, including non ST-segment–elevation myocardial infarction [NSTEMI] and unstable angina), on the other hand, risk stratification has often focused on cardiac markers, electrocardiographic ST-segment depression, and novel risk markers. Indeed, physical examination is often de-emphasized in the evaluation of NSTE-ACS patients.

Khot et al reinstated the importance of physical examination in risk stratification. They analyzed the prognostic value of the admission Killip class on 30-day and 6-month mortality in over 26,000 patients with NSTE-ACS in recently completed trials. As in STEMI patients, advanced age in this cohort was a powerful predictor of higher Killip classification on admission. Higher Killip class patients also had greater comorbidity and were more likely to have ST-segment depression on the electrocardiogram, with elevated enzymes, than Killip I patients. Regardless of whether patients had unstable angina or NSTEMI as their presenting diagnosis, advanced Killip class was a powerful and independent predictor of 30-day and 6-month mortality. Killip II NSTE-ACS was associated with a 3-fold increase in 30-day mortality, and Killip III/IV with a greater than 5-fold increase in short-term mortality compared to Killip I patients. On multivariate analysis, Killip III/IV was the most powerful predictor of mortality at both 30 days and 6 months. Even Killip II was a powerful independent predictor of 30-day and 6-month mortality. The variables providing the greatest prognostic survival data included Killip classification, advanced age, heart rate, systolic blood pressure, and ST-segment depression.

This important analysis shows that physical examination is still vitally important in evaluating and risk stratifying patients with NSTE-ACS. The elderly NSTE-ACS patient is particularly prone to heart failure and hemodynamic compromise. Physical findings, in particular of the lung fields, are critical to determining risk. Advanced age is still an independent risk factor for mortality in this and other studies, such that the increased risk of heart failure in the elderly does not fully account for the high mortality risk in this age group. Certainly until more data are available, aggressive evaluation and management are required in NSTE-ACS patients with heart failure, since such patients are more likely to be elderly and to benefit from coronary revascularization.
Effect of beta-blockade on mortality among high-risk and low-risk patients after myocardial infarction

S. S. Gottlieb, R. J. McCarter, R. A. Vogel


Well-performed randomized controlled trials versus placebo have shown that β-blockade after acute myocardial infarction reduces mortality, sudden cardiac death, and reinfarction. Yet the use of β-blockers after myocardial infarction in the “real world” remains disappointingly low. The Cooperative Cardiovascular Project evaluated the potential benefit of β-blockade from a database comprising demographics, procedures, complications, and discharge medications in 200,000 Medicare patients aged ≥65 years discharged from hospital after surviving acute myocardial infarction in 1994-1995. Among older patients in the cohort, 34% were discharged from hospital on a β-blocker. Lower-risk patients were more likely to leave hospital on a β-blocker than those at higher risk and with more comorbidity. After adjusting for baseline differences in risk profile, 2-year mortality was 40% lower in every subgroup of older patients treated with β-blockade after myocardial infarction than in untreated patients. The absolute 2-year reduction in mortality ranged from 7% to 11%. All subgroups benefited from β-blockade, including all age groups from <70 years to >80 years, and those with prior obstructive lung disease or asthma, diabetes, Q-wave infarction, non-Q-wave infarction, prior heart failure, ejection fraction <20% to >50%, and any treatment received in hospital including coronary artery bypass surgery or angioplasty. This large database of “real world” older patients confirmed the randomized trials. Irrespective of the risk or demographic profile, 2-year survival is tremendously enhanced in this cohort treated with a β-blocker after myocardial infarction.

However, an important caveat applies to early aggressive β-blockade in older patients after acute myocardial infarction. The Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT) Investigators (*Lancet.* 2005;366:1622-1632) randomized nearly 46,000 medically treated patients with acute myocardial infarction (most with ST-segment-elevation myocardial infarction) to intravenous then oral β-blockade or matching placebo on admission. It excluded those with cardiogenic shock. The study was powered to evaluate two primary outcomes, a composite of death, reinfarction, or stroke, and death from any cause during the treatment period (up to 4 weeks). Patients were treated with the study drug for a mean of 15 days. This acute care trial demonstrated no survival advantage and no improved outcome with early aggressive β-blockade compared to placebo. Further analysis showed that for every 1000 patients treated on admission with intravenous then oral β-blockade, 5 fewer patients will reinfarct, 5 fewer will develop ventricular fibrillation, but 11 more will develop cardiogenic shock. All the excess cardiogenic shock in the β-blocker arm occurred on the first hospital day. Since older infarct patients are at increased risk for cardiogenic shock, the important message from this trial is that patient assessment is mandatory before initiating early β-blockade in the acute myocardial infarction setting. A patient with acute myocardial infarction must be hemodynamically stable and free of acute heart failure before initiating β-blocker therapy. Only when an older patient is hemodynamically stable does chronic β-blocker therapy become an important weapon in reducing the risk of death, myocardial infarction, and sudden cardiac death.
Coronary intervention for persistent occlusion after myocardial infarction


**The primary treatment for patients with acute myocardial infarction is rapid opening of the infarct-related artery (IRA). The benefit in restoring coronary patency in patients with ST-segment–elevation myocardial infarction within 12 hours of symptom onset using either percutaneous coronary intervention (PCI) or thrombolytic therapy has been established beyond doubt. There are substantially fewer data regarding the treatment of an occluded IRA in patients presenting late or when an occluded vessel is only discovered on angiography performed beyond the typical time window known to be of clinical benefit. The bias for many physicians has been to open the IRA with PCI even well beyond the 12-hour window from symptom onset. The theoretical reason often cited for this practice includes reduced left ventricular remodeling, improved electrical stability, and the supply of future collateral vessels to other ischemic territories. Although observational data supported this open artery hypothesis, a randomized trial was needed. The Occluded Artery Trial was the answer.**

This critically important trial changed cardiac care for many of our patients. It sought to determine whether late opening of an occluded IRA by PCI changes clinical outcome compared to standard postinfarction therapy. It randomized nearly 2200 patients in whom coronary angiography within 3 to 28 days of myocardial infarction showed an occluded IRA and an ejection fraction <50% or proximal occlusion. Clinically unstable patients were excluded. Most patients receiving PCI were stented; the procedure was successful in establishing coronary flow in 87% of patients, with rare procedure-related complications. The primary end point (a composite of death, nonfatal reinfarction, and New York Heart Association Class IV heart failure during 4 years of follow-up) was similar in the PCI and medical treatment groups. The individual components of the primary end point were also no different between the two groups. There was no significant subgroup interaction between age >65 years or <65 years and the primary end point. In a sub-study in 381 patients undergoing left ventriculography at baseline and at 1 year of follow-up, the primary end point (change in ejection fraction over 1 year) did not differ between the PCI patients and those treated medically.

The Occluded Artery Trial disproved the late open artery hypothesis. It showed that routine PCI on an occluded IRA performed in a time frame beyond myocardial salvage in a stable patient does not decrease clinical events. Any benefits in preventing infarct expansion with a patent IRA may be lost with a higher reinfarction rate in the PCI group. Given that a high percentage of patients enrolled in this trial had collaterals to the IRA at baseline, PCI risked losing those collaterals, thereby increasing the risk of reinfarction with stent thrombosis. Since it is the elderly patient who tends to present to medical attention late after the onset of myocardial infarction symptoms, this study is particularly applicable to the older infarct population. Late opening of an IRA is of no benefit in a stable patient.

The World Chess Champion Vladimir Kramnik loses a match to the Fritz-10 computer program 2-4; a research expedition concludes that the Chinese River Dolphin is probably extinct; and the United Kingdom pays off its World War II debts to the United States and Canada
Ischemic Heart Disease & Chronic Heart Failure in the Elderly

Bibliography of One Hundred Key References

selected by Steven P. Schulman*, MD; Edward G. Lakatta†, MD; Gary Gerstenblith*, MD

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