Angina:
Old Concepts Revisited

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There is no doubt that cardiology is a dynamic subspecialty and that cardiologists are enjoying all the continuous innovations being made available to them. New ideas, new findings, new tools, and new drugs are an almost everyday occurrence. All of these advances assist us in treating classic conditions such as the one that is the focus of this issue of Dialogues in Cardiovascular Medicine: angina. This issue of Dialogues, which takes a fresh look at angina, revisits old concepts, such as revascularization and myocardial ischemia, as well as examining new ones, such as heart rate.

So, if the above about advances assisting us is true in this era of angioplasty and drug-eluting stents, then one has to ask whether angina still exists or whether it has joined the list of rare and orphan diseases. This issue proves the latter way of thinking is wrong; it is still a disease that is very much with us. In most European countries, approximately 20,000 to 40,000 individuals per million suffer from angina, and its prevalence is 10% to 20% in patients aged 65 to 74 years.¹

Nevertheless, in these times of economic crisis, unfortunately what matters most today is the actual cost of angina. Despite the economic burden and the influx of innovative devices—an entirely new generation of stents has been produced, much to the joy of interventionists—no new drugs for the treatment of angina have been developed over the past decade. Curious, isn’t it!

Could the cardiovascular community and pharmaceutical industry have missed something? Indeed, they have. What has been missed is that any angina attack is always preceded by an increase in heart rate. So, why has the importance of heart rate been underestimated for so long? After all, heart rate is the language of the body and the way in which the heart communicates with the world, or rather, the physician.

There is no question that in all medical textbooks, heart rate is thought to have a wide-ranging and complex involvement in several aspects of cardiac function, health,
and disease. However, perhaps due to its familiarity and ease of measurement on the one hand and the complex nature of its effects on the other, the pathophysiological and therapeutic importance of heart rate reduction have not always been fully appreciated.

Interest in the impact of heart rate in cardiovascular disease was given new impetus with the introduction into clinical practice of the specific heart rate–lowering agent ivabradine in 2005. Ivabradine has been shown to be as effective as, if not superior to, high-dose β-blockers or calcium channel blockers in reducing the symptoms of angina. In the angina subgroup of the BEAUTIFUL (morBidity-mortality EvAlUaTion of the I inhibitors) trial, ivabradine improved prognosis and reduced hospitalization for myocardial infarction.

But, perhaps just as important as the therapeutic effects is that the discovery of ivabradine has also ignited interest in the effect that heart rate has on angina and reignited interest in angina itself.

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Angina: old concepts revisited

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Angina pectoris, the most common symptom of coronary artery disease (CAD), currently affects 4% of the population (approximately 12,000,000 persons) in the US and Europe, despite the use of standard therapy. Its pathophysiology has been progressively uncovered, resulting in new therapeutic targets, more effective therapies, and most recently pharmacological, as well as mechanical, measures for altering the natural history of affected patients. Endothelial dysfunction, altered calcium metabolism, systemic inflammatory processes, specific infections, obstructive sleep apnea, and renal dysfunction are now known to affect the development of angina. Though revascularization has long been available to relieve drug-resistant angina, as life spans increase, recurrence commonly occurs. Therapies to deal with this problem include ranolazine, ivabradine, and an old drug, allopurinol. New mechanical therapies, such as spinal cord stimulation and transmyocardial laser revascularization, and emerging biological strategies, like angiogenic gene therapy and stem cell therapy, may also prove useful. A particularly promising approach is pure heart rate reduction. It not only minimizes angina, but appears to minimize the risk of myocardial infarction, death, and heart failure in angina patients. The pathophysiological understanding of angina and angina therapies has progressed substantially in recent years, promising major lifestyle improvements for CAD patients.

For many years, coronary atherosclerosis and consequent myocardial ischemia, with its clinical sequelae, were considered the inevitable result of the aging process. As our understanding of the pathophysiology and pathogenesis of coronary artery disease (CAD) and resulting ischemic heart disease (IHD) progressively improved during the past century, treatment of hypercholesterolemia and hypertension was expected to eliminate CAD and IHD by the year 2000. However, though the latter hope proved illusory, improved understanding of the biology of CAD and IHD has led to new and novel approaches to prevention and, when prevention is inadequate, to treatment. The most common symptom of CAD/IHD is angina pectoris. Despite recent advances, this symptom...
remains quite common, even after mechanical revascularization, and importantly detracts from health-related quality of life (HRQOL). Therefore, approaches to prevention and management of angina are regularly under development.

This article will review new concepts relating to the pathophysiology of myocardial ischemia from CAD (the basis for angina), will place these concepts within the framework of existing knowledge, and will review relatively new and novel approaches to the prevention and management of angina. In this context, we will highlight one of the most exciting of the new developments, the application of a drug (ivabradine) with the sole relevant pharmacological effect of slowing heart rate. Ivabradine has been successfully applied to prevention of angina and has opened a new chapter in the management of patients with angina, with data strongly suggesting a beneficial impact on the natural history of chronic, stable CAD. Since most antianginal drugs never have been assessed for such an effect, the current state of knowledge in this area is of particular importance to the clinician who must manage the patient with angina.

PATHOPHYSIOLOGY—MYOCARDIAL ISCHEMIA AS A MULTIFACTORIAL DISEASE: WHAT IS NEW?

Atherosclerotic lesions are asymmetric focal thickenings of the innermost layer of the artery (Figure 1). They consist of cells, connective tissue elements, lipids, and debris. Blood-borne inflammatory and immune cells constitute an important part of the atheroma, the remainder comprises vascular endothelial and smooth muscle cells. In the center of the atheroma, foam cells and extracellular lipid droplets form a core, surrounded by a cap of smooth muscle cells and a collagen-rich matrix. T cells, macrophages, and mast cells infiltrate the lesion and are particularly abundant in the shoulder region where the atheroma grows. Many of the immune cells exhibit signs of activation and produce inflammatory cytokines. Progressive narrowing of the arterial lumen by the lesion reduces myocardial blood supply, underlying ischemia, and angina. Myocardial infarction (MI) is due to formation of an occluding thrombus on the plaque’s surface caused by plaque rupture or endothelial erosion. Myocardial ischemia is the series of cellular metabolic and functional abnormalities that occur when myocardial oxygen demand outstrips myocardial oxygen supply. The most common underlying factor is an occlusive atherosclerotic arterial lesion sufficient to limit myocardial perfusion/oxygen supply despite compensatory dilatation of arterioles distal to the lesion. Thus, consideration of new concepts regarding ischemia must begin with the lesion.

Conventional risk factors for coronary atherosclerosis

Careful monitoring of the Framingham Study population and parallel groups has identified “major risk factors” or, as they would now be termed, “risk markers”: measurable characteristics that define disease risk. If these can be modified with consequent beneficial modification of the disease, they are properly termed “risk factors.” These include high blood pressure, high blood total (and low-density lipoprotein) cholesterol, smoking, obesity, and diabetes; other risk markers include physical inactivity, abnormal blood triglycerides and subnormal high-density lipoprotein cholesterol, age, sex, and several psychosocial factors. When more than one of these is present, susceptibility to CAD/IHD in-
creases. Indeed, these risk markers cluster and interact multiplicatively to promote vascular risk. Moreover, atherosclerosis is not located only in the epicardial coronary vessels, but is a systemic disease involving all vascular beds and different tissues.

Endothelial dysfunction and coronary atherosclerosis

Deleterious alterations of endothelial physiology, known as endothelial dysfunction, represent key early steps in the development of atherosclerosis and are also important in plaque progression and atherosclerotic complications. Endothelial dysfunction is a result of imbalance of endothelium-dependent vasodilation by either reduction of the bioavailability of vasodilators, particularly nitric oxide, or an increase in endothelium-derived contracting factors. In addition, endothelial dysfunction features endothelial activation, involving proinflammatory, proliferative, and procoagulatory states that favor all stages of atherogenesis. Considering the relationship between endothelial dysfunction and atherosclerosis, an individual subject’s endothelial function probably reflects propensity to develop atherosclerotic disease, and thus may serve as a marker of prognosis.

Figure 1. Atherosclerotic lesion in a human artery. Panel A shows a cross-sectioned coronary artery from a patient who died of a massive myocardial infarction. It contains an occlusive thrombus superimposed on a lipid-rich atherosclerotic plaque. The fibrous cap covering the lipid-rich core has ruptured (area between the arrows), exposing the thrombogenic core to the blood. Trichrome stain was used, rendering luminal thrombus and intraplaque hemorrhage red and collagen blue. Panel B is a high-power micrograph of the area in Panel A indicated by the white rectangle and shows that the contents of the atheromatous plaque have seeped through the gap in the cap into the lumen, suggesting that plaque rupture preceded thrombosis (the black asterisk indicates cholesterol crystals). Panels A and B courtesy of Dr Erling Falk, University of Aarhus, Aarhus, Denmark.) Panel C illustrates the consequences of the activation of immune cells in a coronary plaque. Microbes, autoantigens, and various inflammatory molecules can activate T cells, macrophages, and mast cells, leading to the secretion of inflammatory cytokines (eg, interferon and tumor necrosis factor) that reduce the stability of the plaque. The activation of macrophages and mast cells also causes the release of metalloproteinases and cysteine proteases, which directly attack collagens and other components of the tissue matrix. These cells may also produce prothrombotic and procoagulant factors that directly precipitate the formation of thrombus at the site of plaque rupture.

Under normal homeostatic conditions, the endothelium maintains normal vascular tone and blood fluidity, with no or little expression of proinflammatory factors. However, both conventional and novel cardiovascular risk markers, including smoking, aging, hypercholesterolemia, hypertension, hyperglycemia, family history of premature atherosclerotic disease, obesity, abnormal C-reactive protein, and chronic systemic infection are all associated with endothelial dysfunction, characterized by a chronic inflammatory process accompanied by a loss of antithrombotic factors, increase in vasoconstrictor and prothrombotic factors, and abnormal vasoreactivity, all enhancing risk of cardiovascular events.

At sites of inflammation and injury, reactive oxygen species are generated. At relatively low concentrations, these can function as signaling molecules in regulating fundamental cell activities such as growth and stress adaptation; at higher concentrations, they can cause cellular injury and death. The vascular endothelium, which regulates the passage of macromolecules and circulating cells from blood to tissues, is a major target of oxidative stress, playing a critical role in the pathophysiology of atherosclerosis.

Ryanodine receptor and myocardial ischemia

The sarcoplasmic reticulum (SR) is a target of ischemic myocardial injury. SR dysfunction is believed to be very important in determining cytosolic calcium overload during ischemia and reperfusion. The SR contains calcium ATPase and the SR calcium channel, which corresponds to the ryanodine receptor, both of which are very important in calcium homeostasis. In the absence of ryanodine, the channel undergoes spontaneous openings and closures. The probability of channel opening is a function of local calcium, magnesium, and ATP concentrations. Ryanodine at low concentrations locks the channel in a low-conductivity configuration, and at higher concentrations channel blockade occurs. Interaction with high-affinity channel sites induces formation of the low-conductivity state; interaction with low-affinity sites activates the channel. Ischemia causes significant reduction in high-affinity ryanodine binding sites, persisting even after reperfusion. The mechanisms responsible for receptor alteration are unclear, but may include changes in redox potential, intracellular acidosis, exposure to reactive oxygen species, proteolysis, phosphorylation or dephosphorylation or modification of receptor interaction with the SR membrane. These changes occur early during ischemia, before irreversible cellular injury (most reduction in ryanodine binding occurs in the first 10 minutes of ischemia). Reduction in active SR channels might decrease calcium availability, which may characterize the late phase of stunning. Given the apparent role of cytosolic calcium overload in the pathogenesis of irreversible tissue injury, the reduction in ryanodine receptors with ischemia could be related to ischemic preconditioning, ie, to the reduced susceptibility of the posts ischemic myocardium to further ischemic injury.

Systemic inflammatory process and coronary atherosclerosis

Patients with coronary atherosclerosis manifest abnormal blood concentrations of inflammatory cytokines and other acute-phase reactants. For example, concentrations of CRP and interleukin-6 are abnormal in patients with unstable angina and MI; prognosis is worse as concentrations increase. The concentrations of other inflammatory markers are also abnormal in these patients, including fibrinogen, interleukin-7, interleukin-8, soluble CD40 ligand, and the CRP-related protein pentraxin 3. A moderately abnormal CRP level on a highly sensitive immunoassay is an independent risk marker for CAD in a healthy population. Other measures of acute-phase reactants, including the erythrocyte sedimentation rate and concentrations of fibrinogen and other plasma proteins, also provide information about the risk of CAD, as do concentrations of circulating adhesion molecules such as soluble intercellular adhesion molecule–1 (ICAM–1), soluble vascular cell adhesion molecule–1 (VCAM–1), and soluble P-selectin, which are shed by activated cells. Since several different inflammatory markers, with different biologic activities, contribute to the risk of CAD, it is unlikely that any of them actually causes the disease, but rather they reflect the local and systemic inflammatory process in the artery and other tissues. Inflammation may promote cardiovascular disease by enhancing endothelial dysfunction, arterial stiffness, and atherosclerotic lesions directly, but also by accentuation of conventional risk factors, such as serum lipids, insulin resistance, or blood pressure.

Patients with rheumatoid arthritis or other inflammatory arthropathies (eg, ankylosing spondylitis, psoriatic arthritis) have a higher risk of cardiovascular disease than those without these conditions. The excess risk cannot be fully explained by conventional risk markers; several studies suggest that the systemic inflammatory burden of these arthropathies accelerates ath-
Obstructive sleep apnea and coronary atherosclerosis

Obstructive sleep apnea (OSA) is now recognized as an independent risk factor for hypertension. Treatment of OSA with continuous positive airway pressure (CPAP) has reduced blood pressure. OSA manifests many features in common with metabolic syndrome, including systemic hypertension, central obesity, and insulin resistance. In a controlled study of patients with OSA treated with nasal CPAP, Brooks et al showed improved insulin sensitivity, while weight and drug treatment remained stable. In OSA, cyclical variations in heart rate and blood pressure are dramatic and occur during sleep, when blood pressure and heart rate normally are the lowest and least variable. The association of metabolic syndrome and OSA tends to confound studies looking at independent effects of OSA on vascular disease.

Abnormal sympathetic nervous system activity, a cardinal feature of OSA, results from the interaction of several excitatory mechanisms normally dormant during sleep. The pulmonary stretch receptor reflex that normally suppresses central sympathetic discharge ceases during apnea, disinhibiting central sympathetic outflow. The ensuing hypoxia and hypercapnia further augment sympathetic activity by stimulating peripheral and central chemoreceptors. The resulting vasocostriction raises peripheral resistance, while increased cardiac sympathetic stimulation increases heart rate and reduces heart rate variability.

Although arousal from sleep at the termination of an apneic episode facilitates airflow resumption, the resulting excitatory input from cortical centers will cause a further burst of sympathetic outflow and loss of vagal tone. The immediate postapneic period is therefore characterized by profound surges in blood pressure and heart rate. In severe OSA, cycles of apnea and arousal can recur several hundred times each night, exposing the heart and circulation to high amplitude oscillations in central sympathetic nerve traffic, blood pressure, and heart rate. The adverse effects of obstructive apnea on the cardiovascular system are not confined to sleep. Daytime sympathetic nervous activity and systemic blood pressure are increased in patients with OSA. There also appears to be a sustained reduction in vagal tone in patients with OSA, exemplified during wakefulness by a reduction in total heart rate variability.

In OSA, abnormal peripheral sympathetic nerve activity persists during wakefulness and may affect acute coronary events in the early hours of the day. Suzzaman et al. found that, compared with control subjects matched for age, sex, and body mass index, patients with OSA had higher plasma CRP concentrations that were proportional to the frequency of apneas and hypopneas. Patients with OSA also demonstrated increased oxidative stress. In patients with OSA and coexisting CAD, oxidative stress is associated with abnormal levels of ICAM-1, VCAM-1, and E-selectin. In a tightly matched case-control study, OSA was confirmed as an independent predictor of CAD, with an odds ratio (OR) of 3.1.

At long-term follow-up, subjects with CAD whose OSA remained untreated had higher mortality than those who were treated. Many data suggest that OSA is a novel cardiovascular disease risk factor, however, it will take a series of studies to bridge the gaps in our knowledge in this area.
Renal failure and coronary atherosclerosis

Cardiovascular diseases are the leading cause of death (30% to 50% of all deaths) in patients with end-stage renal disease. Impaired endothelium-dependent vasodilation is associated with renal dysfunction attributed variously to oxidative stress, hyperhomocysteinemia, dyslipidemia, hyperglycemia, hypertension, and retention of L-arginine inhibitors. Statins have not been successful in primary prevention of CAD in renal failure, suggesting an uncommon pathophysiological basis for the accelerated atherogenesis, possibly related to variation in calcium-phosphate metabolism.

Summary

Recent evidence suggests that several processes, relatively ignored in an earlier era, are probably central to the development of the atherosclerotic lesions underlying angina and, in some cases, important in directly modulating the relation of myocardial oxygen supply and demand, imbalance of which is the direct cause of angina. These processes include endothelial function, mitochondrial calcium metabolism, systemic inflammation, infection with some group of microorganisms, OSA, a common condition linked by several metabolic and mechanical factors to both atherosclerosis and ischemia, and renal dysfunction (which, when present, probably importantly modulates the fundamental pathophysiology of atherosclerosis). Additional research in these and other emerging areas may provide new targets for therapy of angina and for prevention of its underlying basis.

TREATMENT—ANGINA PREVENTION AFTER REvascularization: WHAT IS NEW?

As previously indicated, angina is the most common symptom of CAD and is the predominant cause of angina. Despite improvements in therapy during the past 4 decades, angina continues to limit lifestyle in patients with CAD. 300 000 to 900 000 patients in the US, and the same number in Europe, have angina refractory to standard therapy, between 25 000 and 75 000 new cases are diagnosed each year. Angina is the presenting symptom in 50% of those with CAD. Most often, angina is “stable,” ie, after its onset, it occurs at relatively predictable workload, frequency, and severity. The consensus definition of “stability” requires that the symptom must change little in these characteristics over 2 weeks, though some variation occurs if activity, ambient temperature, etc, change myocardial oxygen demand. In general, stable angina implies stability of the underlying atherosclerotic plaque. Changes in plaque architecture, including rupture or superimposed thrombosis, tend to occur rapidly or relatively suddenly. Almost 20% of acute MI is preceded by chronic stable angina.

Current preventive strategies include pharmacotherapy, revascularization (percutaneous coronary intervention [PCI] or coronary artery bypass grafting [CABG]) or other mechanical interventions. Due to its invasive nature, revascularization is often reserved for patients refractory to pharmacotherapy. PCI reduces angina frequency compared with medical therapy, but this benefit wanes with time. Months after angioplasty, angina persists in 36% of patients. Recently, the MASS-II (Medicine, Angioplasty or Surgery Study II) study and COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive drug Evaluation) trials compared angina prevention with PCI versus pharmacological therapy (and CABG) in stable CAD. In MASS-II, after 1 year of follow up, 79% of those undergoing PCI, 88% of those with CABG, and 46% with pharmacotherapy alone were angina free, though no differences were found in mortality. In COURAGE, at 1 and 3 years, freedom from angina was greater after PCI than after medical therapy alone, but at 4.7 years, 74% post-PCI and 72% solely receiving drugs were angina free. Thus, despite angina-relieving efficacy, PCI or CABG eventually require adjunctive antianginal therapy.

The aim of this section will be to review options for angina prevention after revascularization. These include pharmacological therapy (ranging from the most commonly employed agents [β-blockers, calcium channel blockers, and long-acting nitrates] to less commonly used drugs [ranolazine, ivabradine, and allopurinol, all relatively new approaches, and nicorandil, fasudil, and trimetazidine, all long available or unproven], mechanical therapy other than revascularization [carotid sinus nerve stimulation, and largely abandoned, enhanced external counterpulsation, and transcutaneous nerve stimulation, available for many years without strong data support, and spinal cord stimulation and transmyocardial revascularization (TMR), relatively more recent, but little used] and biological therapy [angiogenic gene therapy and stem cell therapy]). Supporting data only for the more recent (“new”) therapies will be reviewed herein. Importantly, in the current era, by consensus all patients with angina should also receive therapies shown to minimize progression of CAD and its sequelae, including antiplatelet...
therapy (aspirin, clopidogrel or, perhaps, newer agents), ramipril, perindopril, or perhaps telmisartan for secondary coronary event prevention, aggressive lipid management, mitigation of hypertension and of diabetic glucose metabolism.

New pharmacological therapies

Ranolazine

Ranolazine is a piperazine derivative, approved by the US Food and Drug Administration (FDA) as well as the European Medicines Agency (EMA) for add-on use when angina is not adequately controlled with established therapies. The antianginal and anti-ischemic effects may result from several pharmacological actions, including altered myocyte metabolism to favor oxidation of glucose over fatty acids by partial fatty acid oxidation (p-FOX) and reduction in myocyte calcium overload through inhibition of the late sodium current (I_{Na}). The drug also has modest α- and β-blocking properties.

Ranolazine dose-dependently increases total exercise duration and time to 1-mm ST-segment depression both as monotherapy and in combination with atenolol and decreased diary-reported angina frequency with background amlodipine, atenolol, or diltiazem. In the placebo-controlled CARISA (Combination Assessment of Ranolazine In Stable Angina) trial, maximal benefit was achieved with a dose of 750 mg twice daily with no additional benefit from a higher dose. The MERLIN-TIMI-36 (Metabolic Efficiency with Ranolazine for Less Ischemia in Non-ST-elevation acute coronary syndromes–Thrombolysis in Myocardial Infarction–36) trial randomized 6560 patients with acute coronary syndromes to intravenous ranolazine or a placebo, in addition to standard therapy. Ranolazine was administered as a bolus of 200 mg over 1 hour and then continued as an infusion for 12 to 96 hours, followed by 1000 mg orally twice daily. After a median follow-up of 348 days, ranolazine showed no effect over placebo on all-cause mortality, sudden cardiac death, or frequency of symptomatic arrhythmias. However, the drug reduced angina frequency and demonstrated an overall favorable safety profile. This was very important for its FDA approval because of prior concerns about drug-induced syncope and electrocardiographic QT prolongation, concerns ameliorated by MERLIN-TIMI-36. Adverse effects (primarily dizziness, nausea, asthenia, and constipation) appear to be dose related. In clinical trials, fewer than 8% of patients discontinued ranolazine due to adverse effects; most withdrawals occurred at 1500 mg twice daily, higher than the dose shown to be maximally effective. As a result, the approved starting dose is 500 mg twice daily, with possible up titration to 750 mg twice daily and 1000 mg twice daily if lower doses do not adequately prevent angina. An extended-release oral preparation is also available.

Ivabradine (Procoralan)

Ivabradine is a selective heart rate–lowering agent. Heart rate slowing has long been understood to be effective in preventing angina and is the major determinant of myocardial oxygen demand, thus, it is expected that its increase beyond some threshold value should precipitate ischemia or angina. Heart rate also predicts outcome in epidemiologic studies of patients with CAD as well as other cardiovascular conditions (eg, heart failure and hypertension), the relation of heart rate and outcome also has been observed in otherwise healthy, free-living cohorts. The published basis for the use of a pure heart rate–slowing agent for angina prevention and for beneficial alteration in the natural history of patients with CAD and angina will be presented in detail in the next section.

Allopurinol

Allopurinol is a xanthine oxidase inhibitor long used for uric acid reduction in patients with gout. The drug also has anti-ischemic effects, possibly attributable to inhibition of xanthine oxidase–derived reactive oxygen species generation with injury via ATP catabolism during hypoxia, inhibition of lipid peroxidation, heat shock factor expression, calcium sensitizing, and cellular antioxidant potentiation. A recent randomized placebo-controlled crossover study by Noman et al suggested that allopurinol is an effective antianginal, anti-ischemic agent. These investigators enrolled 65 patients with angina and angiographically proven CAD and assigned them at random to placebo or allopurinol (600 mg per day) for 6 weeks before crossover. During treadmill exercise testing, high-dose allopurinol significantly prolonged time to ST-segment depression, total exercise time, and time to angina onset. These results suggest that endogenous xanthine oxidase activity may contribute to exercise-induced myocardial ischemia. Experimental data suggest that allopurinol therapy has a beneficial effect on endothelial function. The main side effects were gastrointestinal distress, hypersensitivity reactions, and skin rash. Allopurinol has not been FDA- or EMA-approved for use as an antianginal medication.

Uric acid has been associated with variety of cardiovascular conditions including hypertension, metabolic syndrome, CAD, cerebrovascular disease, and vascular
dementia. Although evidence is mounting that uric acid is a risk factor for CAD, there are insufficient data to recommend treatment of asymptomatic hyperuricemia. Potential mechanisms by which elevated uric acid is related to cardiovascular disease are illustrated in Table I.

New mechanical therapies

Spinal cord stimulation
Spinal cord stimulation (SCS) or dorsal column stimulation or neurostimulation, alleviates pain by electrically activating pain-inhibiting neuronal circuits in the dorsal horn and inducing paresthesia that masks the original pain sensations. The magnitude of stimulation is regulated by the patient using a remote control device. The mechanism underlying SCS is not fully understood. Benefit has been attributed to decreasing pain and sympathetic tone to reduce myocardial oxygen consumption and improved myocardial microcirculatory blood flow. SCS has demonstrated effectiveness and acceptable safety among patients with refractory angina who are unresponsive to medical and surgical intervention. However, SCS may interfere with pacemaker and/or implantable defibrillator function by inappropriately inhibiting pacemaker signals, though cautious and careful monitoring may minimize this risk.

A meta-analysis of 7 randomized controlled trials involving 270 patients found enhanced exercise tolerance and health-related quality of life (HQOL) that paralleled those associated with CABG and percutaneous myocardial laser revascularization (PMR). However, the trials were small and some were questioned as to quality. As with almost all device-based trials, interpretation of data is confounded by lack of blinding (effective SCS produces paresthesia in the area of the pain). Nonetheless, a recent randomized single-blinded multicenter trial involving 25 patients divided into 3 groups (paresthetic SCS, nonparesthetic SCS, and sham SCS) reported that SCS with chest paresthesia resulted in significant improvement in angina episodes, nitroglycerin consumption, and angina class at 1 month of therapy. Reduction in anginal attack rate persisted for 3 months.

The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines for the management of patients with chronic stable angina provided a Class IIb recommendation for this modality, suggesting that SCS should only be used in patients who cannot be managed adequately by medical therapy and who are not candidates for revascularization.

- Hypertension and prehypertension
- Renal disease (including reduced glomerular filtration rate and microalbuminuria)
- Metabolic syndrome (including abdominal obesity, hypertriglyceridemia, low level of high-density lipoprotein cholesterol, insulin resistance, impaired glucose tolerance, elevated leptin level)
- Obstructive sleep apnea
- Vascular disease (carotid, peripheral, coronary artery)
- Stroke and vascular dementia
- Preeclampsia
- Inflammation markers (C-reactive protein, plasminogen activator inhibitor type 1, soluble intercellular adhesion molecule type 1)
- Endothelial dysfunction
- Oxidative stress
- Sex and race (postmenopausal women, blacks)
- Demographic (movement from rural to urban communities, Westernization, immigration to Western cultures)

Table I. Cardiovascular conditions and risk factors associated with elevated uric acid.

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Transmyocardial revascularization
TMR has been developed and evaluated during the last 20 years specifically for patients with refractory angina. TMR involves application of high-energy laser beams to create a series of nontransmural endomyocardial channels. These channels can be generated surgically, using an epicardial approach, or percutaneously via PMR, via catheter, using an endocardial approach. The basis for angina prevention with TMR is unclear. Initially it was believed that the channels directly perfused the myocardium with oxygenated blood from the left ventricle. However, support for this mechanism is relatively weak. Alternatively, TMR may stimulate angiogenesis, cause a marked placebo effect, or destroy myocardial afferent fibers that carry pain signals. TMR also has been used to administer angiogenic growth factors and/or angiogenic gene vectors to stimulate angiogenesis (see biological therapy, below).

Early encouraging results led to consideration of TMR as a useful therapy for patients with angina inadequately responsive to medication who could not undergo conventional revascularization. However, subsequent randomized controlled trials have failed to support the early enthusiasm.
Angiogenic gene therapy

The theoretical capacity to stimulate formation of new blood vessels (angiogenesis) from preexisting vessels has been supported by experimental evidence and has led to intensive efforts to develop applications for clinical medicine. Angiogenesis is strongly, if circumstantially, associated with repeated myocardial ischemia in chronic CAD. For therapeutic application, stimulation of the process with drugs or biological agents would be most useful. Indeed, experimental evidence supports this approach, early clinical research suggests that molecular stimulation with growth factors can enhance jeopardized blood supply, relieve ischemia, improve regional and global LV performance, reduce angina, and improve clinical outcomes. Growth factors can stimulate blood vessel growth in humans. Several have been employed in studies of angiogenic gene therapy, including fibroblast growth factors, vascular endothelial growth factors, and granulocyte/macrophage colony-stimulating factor (GM-CSF). The mode of delivery initially was via systemic or intracoronary infusion, but results have not been encouraging, possibly due to the short residence time of the infused proteins at tissue targets. Repeated administration or prolongation of target residence with sustained release polymers may be helpful, but these approaches have not yet been tested. Direct introduction of the relevant genes into the myocardium might overcome the delivery problems and the safety concerns associated with high concentrations of short-lived blood-borne proteins. Both plasmids and adenoviruses have been used as vectors to introduce the candidate genes, with some improvement in heart function and in myocardial perfusion having been reported experimentally.

For angina and ischemia reduction in humans, this promising approach has, as yet, provided mixed results in terms of alterations in myocardial perfusion, exercise capacity, angina reduction, time to ST-segment change, and exercise tolerance.

Stem cell therapy

Bone marrow-derived hematopoietic stem cells can potentially differentiate into multiple cell types, including those involved in angiogenesis. Stem cells can be harvested from the bone marrow or from peripheral blood (by apheresis). Before attempting harvest, stem cell production usually is stimulated with GM-CSF. Cardiac stem cell therapy has been evaluated clinically during the past 10 years, most often for treatment of heart failure and acute MI. Stem cell therapy for refractory angina now is also under study, initially with angiogenic growth factors released by bone marrow cells. Thus, Losordo et al. has reported angina prevention after intramyocardial transplantation of autologous GM-CSF–mobilized peripheral blood CD34+ stem cells. In a recent phase 2 trial, 167 patients were randomized to receive either low- or high-dose autologous CD34+ cells or an equal volume of diluent alone.
At 6 and 12 months after therapy, diary-reported angina frequency and exercise tolerance were significantly better in the low-dose group than with placebo. Mortality at 12 months was 5.4% in the placebo group, but no deaths had occurred among treated patients, though introduction of the stem cells was associated with cardiac enzyme elevation in 4.6% of treated patients. Intracoronary administration of autologous CD34+ cells also has been demonstrated to be feasible and acceptably safe and, in the initial report, was associated with reduction in angina and nitroglycerin consumption and with improved exercise time at 6 months in patients with intractable angina. Stem cell therapy, though investigational at present, holds great promise for treatment of refractory angina. Initial results support optimism. However, the magnitude, consistency, and durability of antianginal benefit and the long-term safety of this modality remain to be determined.

Summary

Although revascularization is associated with reduction in angina among patients for whom results of medical therapy alone are inadequate, many patients continue to have angina despite revascularization. In addition, revascularization tends to lose its effect over time, and cannot be repeated indefinitely. Thus, new approaches, including new conventional antianginal drugs, as well as novel mechanical and biological approaches, must be explored. Results with some of these approaches are promising, but considerable work remains before they can enter routine clinical practice.

ANGINA AND HEART RATE: WHAT IS NEW?

As previously indicated, the role of heart rate modulation in preventing angina has been well established. Heart rate is the major determinant of myocardial oxygen demand; thus, it is expected that its increase beyond some threshold value should precipitate ischemia or angina. The recent introduction of a pure heart rate–slowing drug, ivabradine, has confirmed the utility of heart rate reduction in preventing angina and has provided new experimental support for the apparent underlying mechanisms. Most recently, however, great interest has developed concerning the role of heart rate modulation in altering the natural history of patients with CAD and, most particularly, with angina. The previous section briefly reviewed the utility of ivabradine in treating patients with angina. This section will focus more fully on the data now suggesting the particular utility of heart rate modulation in preventing angina, on heart rate as a risk factor in patients with CAD and angina, and, therefore, on the possible benefit of heart rate modulation on clinical outcomes for CAD/angina.

Evidence for pure heart rate–modulation therapy for angina and ischemia prevention

Despite availability of multiple antianginal drugs and mechanical therapy, angina remains very common in patients with CAD, affecting 30% to 50% of such individuals. Currently, drug therapy intended for angina prevention is based predominantly on β-blockade and, to a lesser extent, on calcium channel blockade or administration of long-acting nitrates. The first of these groups virtually always modulates heart rate; the second usually does when the drug is a nondihydropyridine. However, all conventional antianginals are associated with many untoward effects in patients with angina and often may not be tolerated at effective doses; indeed, current European registry data indicate that, among patients receiving β-blockers for angina prevention, 50% have stopped this therapy within 2 years of prescription. In heart failure management (the majority of cases are of ischemic cause), about 30% of patients are considered to be intolerant of β-blocker therapy. Ischemia and resulting angina from CAD develop from myocardial oxygen supply–demand imbalance. Therapy for patients with CAD and angina aims to restore this balance. The major determinants of myocardial oxygen demand are heart rate, systolic blood pressure, and contractility. Indeed, increase in heart rate is a precipitating factor for ischemia or angina. Experimentally, a twofold increase in any of these determinants of oxygen consumption requires an approximately 50% increase in coronary blood flow if ischemia is to be avoided. The primary determinants of myocardial oxygen supply are coronary artery patency, perfusion pressure, arterial oxygen content, and duration of diastole, when coronary flow occurs. Oxygen extraction by myocardial tissue is relatively high even at rest. Therefore, needed increases in myocardial oxygen consumption require increases in coronary flow and oxygen delivery.

Ivabradine

Ivabradine is a selective heart rate–lowering agent with primary pharmacological action on the inward sodium–potassium \( I_{f} \) current generated specifically in the sinoatrial (SA) node (Figure 2). The \( I_{f} \) current, discovered in 1979 by DiFrancesco et al, is of rela-
tively low amplitude and is the primary modifier of the spontaneous depolarization rate of SA node myocytes. In blocking this current, ivabradine slows the heart rate. Its effect is greatest when the number of open If-channels is greatest (ie, when heart rate is highest). Therefore, ivabradine lowers heart rate most effectively and to the greatest extent when pretherapy heart rate is fastest. This property is called “use dependence” and confers relative freedom from excessive bradycardia when the drug is used alone or when it is used with other heart rate–slowing agents (see below). Unlike beta-blockers, ivabradine has no effect on inotropy, lusitropy, or atrioventricular nodal conduction.

Slowing heart rate increases the proportion of the cardiac cycle occupied by diastole, when coronary flow occurs, thus permitting enhancement of myocardial oxygen supply at the same time demand is decreased by heart rate slowing. Indeed, experimentally, doubling heart rate from 80 bpm to 160 bpm, by itself results in a 2.5-fold decrease in diastolic duration, with associated reduction in coronary flow reserve (Figure 3). The lack of inhibition of inotropy and lusitropy is similarly important. Beta-blockers, which depress both, presumably increase myocardial oxygen consumption and decrease coronary vasodilator reserve.

In addition, unlike some beta-blockers, pure heart rate slowing with ivabradine does not cause coronary vasoconstriction. Experimentally, during exercise, propranolol reduces coronary diameter by approximately 6%, while ivabradine is associated with a 1%-2% increase, indistinguishable from the effect of saline infusion. The result is greater coronary flow reserve with pure heart rate slowing than with heart rate slowing mediated by beta-blockade.

![Figure 2. Potential role of heart rate in cardiovascular pathology.](image)

High heart rate is a risk factor for the development of atherosclerosis. High heart rate leads to ischemia, remodeling of heart and vessels, and contributes to comorbidities in hypertension and chronic heart failure. Figure shows potential mechanisms with experimental or clinical evidence. If channels are exclusively located in sinoatrial node and are responsible for inwardly directed current, which accelerates diastolic depolarization of sinus node and thus its pacemaker function. The If channel can be inhibited by ivabradine. Green dots = If current.


![Figure 3. Relationship between heart rate and diastolic time.](image)

In one study, when heart rate was slowed to a similar extent by atenolol and by ivabradine, coronary flow was 40% higher with the pure heart rate–slowing drug than under β-blockade. Thus, it is not surprising that ivabradine is effective and acceptably safe for prevention of angina in patients with CAD. Indeed, the utility of ivabradine for preventing angina and ischemia has been demonstrated in multiple trials, both when the drug is used as monotherapy and when it is used in combination with other antianginals. A randomized, double-blind placebo controlled trial of ivabradine as monotherapy involved 360 patients with chronic stable angina. In this study, ivabradine increased time to limiting angina and time to onset of 1-mm ST-segment depression compared with placebo during formal bicycle exercise testing and significantly decreased diary-reported angina compared with baseline (Figure 4). As monotherapy, the drug also was noninferior to the β-blocker atenolol (Figure 5).

Thus, INITIATIVE (INternational Trial on the Treatment of angina with IVabradinE versus atenolol) demonstrated a nominal increase in exercise tolerance compared with atenolol, though this difference was not statistically significant, and showed little difference in time to 1-mm ST-segment depression. All these comparisons with atenolol were highly significant for noninferiority to the β-blocker. Like atenolol, ivabradine also reduced spontaneous angina episodes compared with baseline. The specific increment in exercise duration was assessed as a function of heart rate reduction; this parameter might be termed antianginal efficiency. In this comparison, ivabradine markedly and significantly outperformed atenolol. When compared with amlodipine using treadmill exercise, ivabradine was noninferior in improving exercise tolerance and in increasing time to 1-mm ST-segment depression.

In theory, excessive bradycardia might be expected when ivabradine is combined with a β-blocker. However, this was not found in the ASSOCIATE (evaluation of the Antianginal efficacy and Safety of the aSsociation Of the I I Current Inhibitor ivAbradine with a beTa-blockE) trial in which ivabradine was compared with placebo on a background of atenolol. In this study of more than 900 patients, ivabradine significantly outperformed placebo (Figure 6) and symptomatic bradycardia was rare, as expected, because of ivabradine’s “use dependence.” Moreover, across all angina prevention trials, ivabradine manifested consistent efficacy among all subpopulations and all cohorts. In terms of diary-reported anginal episodes, frequency consistently decreased with ivabradine, from 51% to 70%. 

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**Figure 4.** Effects of ivabradine on exercise tolerance test at trough of drug activity. Modified from reference 80: Borer et al. Circulation. 2003;107:817-823. © 2003, American Heart Association, Inc.

**Figure 5.** Efficacy of ivabradine versus atenolol on total exercise duration at trough. Abbreviations: od, once daily; bid, twice daily. Modified from reference 79: Tardif et al. Eur Heart J. 2005;26:2529-2536. © 2005, The European Society of Cardiology.
Ivabradine is well tolerated. The primary side effect is relatively infrequent transient and reversible “phosphenes” (flashing scotomata), that are sufficient to cause cessation of therapy in less than 1% of patients. This symptom is attributed to ivabradine-mediated blockade of the retinal h channels, similar to the SA nodal f channels. In addition, compared with placebo, it causes only a relatively small excess risk of symptomatic or dose-limiting bradycardia. Ivabradine has not yet been presented to the FDA, but is approved in Europe and elsewhere and is widely used in many countries.

**Evidence for heart rate as a risk marker in CAD**

Epidemiologically, self-reported angina substantially increases the risk of coronary events compared with its absence. Risk is even higher if angina is associated with exercise-induced ischemia on formal evaluation. Though never specifically studied, it seems highly likely that heart rate adds to the predictive value of angina for events. Thus, during the past 65 years, multiple epidemiological studies have established heart rate as a risk marker for cardiovascular events and for total mortality in cohorts with CAD (as well as with hypertension, heart failure, and unselected insurance cohorts or groups without apparent disease). There is an experimental basis for this relation. Thus, tachycardia potentiates the development and progression of atherosclerosis. It has been suggested that this phenomenon results from the direct relation of heart rate and hemodynamic shear stress. The latter, in turn, may result from shortening of diastole and changes in flow direction, which may damage intercellular junctions and thus increase endothelial cell permeability, facilitating the ingress of atherogenic particles into the tunica media. Tachycardia also tends to increase mean arterial pressure by shortening diastole (with associated increase in pulse pressure), consequently increasing cardiac workload and thickening arteriolar smooth muscle. Heart rate also is inversely related to arterial compliance. Studies in experimental animals support the relation between heart rate and CAD. Beere et al studied a cohort of monkeys fed an atherogenic diet for 6 months; these investigators then ablated the sinus node in half the monkeys. The controls, which manifested persistently higher heart rates than the ablated group, revealed significantly more coronary artery atherosclerotic lesions than the ablated animals. Similar relations have been reported in other studies.

Progression of coronary atherosclerosis has also been associated with heart rate in humans. Perski et al observed that heart rate on 24-hour ambulatory electrocardiography predicted progression of CAD, independently of, and with better predictive value than, conventional risk factors. Similarly, Huikuri et al reported an association between heart rate and progression of focal coronary atherosclerosis in patients with coronary artery bypass grafts.

The prognostic importance of heart rate in patients with chronic CAD and those surviving after MI has been demonstrated in several studies. In a large cohort hospitalized for acute MI in Israel in 1985-1986, Disegni et al found on multivariate analysis that heart rate at admission was an independent predictor of in-hospital and 1-year postdischarge mortality. The Coronary Artery Surgery Study (CASS) registry reported long-term outcome and related this to resting heart rate at study entry in approximately 25,000 patients with known or suspected CAD. Cardiovascular mortality varied directly with resting heart rate at study entry.
≥83 bpm was a strong predictor of overall (hazard ratio [HR], 1.32; 95% CI, 1.19-1.47; P<0.0001) and cardiovascular mortality (HR, 1.31; 95% CI, 1.15-1.48; P<0.0001), independent of known risk markers such as hypertension, diabetes, smoking, LV ejection fraction, and number of hemodynamically significantly diseased coronary vessels. In the INternational VErapamil-SR/trandolapril STudy (INVEST) trial in patients with hypertension and CAD, resting heart rate at entry and at follow-up was directly associated with risk of adverse outcomes. Hjalmarson et al reported that heart rate of patients with MI recorded at hospital admission is directly related to all-cause mortality at 1 year (14% when admission heart rate was <60 bpm, 41% when admission heart rate was ≥90 bpm, and 48% when admission heart rate was >110 bpm).

![Figure 7](image_url)

**Figure 7. Increased heart rate and risk of cardiovascular events.** Heart rate ≥70 bpm increases risk of cardiovascular events (death, hospitalization for heart failure, hospitalization for fatal or nonfatal myocardial infarction).

**Abbreviations:** bpm, beats per minute; MI, myocardial infarction.


Meta-analyses of the GISSI-2 and GISSI-3 trials (Gruppo Italiano per lo Studio della Streptochinasin nell’Infarto miocardico 2 and 3), involving approximately 20,000 patients, found that in-hospital mortality after MI rose from 3.3% for patients with admission heart rate <60 bpm to 10.1% for patients with admission heart rate >100 bpm, and that both mean heart rate and failure of heart rate to fall between hospital days 1 and 7 is prognostically a poor response. Heart rate also is prognostically valid in patients with ST-segment–elevation myocardial infarction (STEMI) who undergo primary PCI. 6-month follow-up data from 2477 consecutive patients with STEMI treated by primary PCI revealed more than twofold greater mortality when heart rate was >80 bpm than when heart rate was lower. Among the 10,917 patients with stable CAD, LV ejection fraction <40%, and no more than mild-to-moderate heart failure in the BEAUTIFUL (morbidity-mortality EventUa- tion of the I 
 inhibitor ivabradine in patients with coronary disease and left-ventricular dysfunction) trial, natural history was assessed in the 5438 patients randomized to the placebo arm. They were divided for analysis into those with heart rate ≥70 bpm and <70 bpm at study entry. The group with higher heart rate had 34% greater cardiovascular death, 53% more hospital admissions for heart failure, 46% more MI, and 38% more revascularizations than those with lower heart rate (Figure 7). These findings were similar to those reported almost simultaneously from a post hoc analysis of the TNT trial (Treating to New Targets). In that study, analysis of 9580 subjects followed for a median of 4.9 years revealed a major cardiovascular event rate of 11.9% in those with entry heart rate ≥70 bpm and an event rate of 8.8% in those with entry heart rate <70 bpm. In summary, heart rate is a risk marker in patients with CAD as in other populations.

**Evidence for heart rate as a risk factor in CAD**

Though heart rate is directly related to adverse outcome in patients with CAD, ie, it is a risk marker, evidence that it is a risk factor, ie, that its modulation leads to modification of natural history, was indirect until the recent availability of ivabradine to slow heart rate without affecting other cardiovascular characteristics. As a risk factor, heart rate has a distinct advantage: it is easily accessible for simple measurement. Heart rate control can be achieved with β-blockers and certain calcium channel blockers. However, these drugs—though currently the primary therapies for angina prevention worldwide—can also cause adverse effects, often sufficient to limit their dose or to preclude their use completely. Moreover, neither β-blockers nor calcium channel blockers have ever been studied for their effects on outcome in patients with chronic stable CAD, with or without angina.

Indeed, among antianginal drugs, ivabradine has been relatively unique in demonstrating natural history improvement as well as symptom-relieving benefits in patients with chronic, stable CAD with (and without) angina. The single example of such benefit with another antianginal drug was demonstrated with nicorandil, an antianginal not approved in the US, but shown in the IOONA trial (Impact Of Nicorandil in Angina) to improve outcome primarily by reducing development of accelerated angina compared with placebo in patients with chronic stable disease at study entry.
In the BEAUTIFUL trial, performed on a background of each patient's usual therapy (including β-blockers, calcium channel blockers, statins, angiotensin-converting enzyme inhibitors, antiplatelet drugs, etc), analysis for relation of drug with outcome was prospectively applied to the entire cohort and, additionally, to patients with heart rate ≥70 bpm before therapy. The latter analysis was based on the TNT epidemiological data, which indicated a relation of survival to heart rate with an asymptote of 70 bpm. Among the subset with heart rate ≥70 bpm, heart rate reduction with ivabradine markedly and significantly reduced the incidence of fatal or nonfatal MI (by 36%, \( P=0.001 \) vs placebo), as well as the incidence of revascularization and non-MI acute coronary syndrome, though the trial’s primary end point (cardiovascular death plus non-fatal myocardial infarction plus hospitalization for heart failure) was not significantly altered.\(^{84}\) Perhaps more importantly, in a post hoc analysis among the 1507 BEAUTIFUL patients who entered the trial with stable angina pectoris, ivabradine was associated with a marked and statistically significant (24%, \( P=0.05 \)) reduction in the primary outcome across the entire heart rate spectrum, most pronounced (31% reduction) among those with heart rate ≥70 bpm.\(^{151}\) Parenthetically, the validity of heart rate as a risk factor also was supported by the recent SHIFT (Systolic Heart failure treatment with the \( I_f \) inhibitor ivabradine Trial) study in 6505 patients with heart failure, two thirds of whom had CAD.\(^{152}\)

**Figure 8. Effect of ivabradine on reduction of primary end point in subgroup of patients from the BEAUTIFUL study.**

Kaplan-Meier time-to-event curves by treatment group for composite primary end point (cardiovascular death, hospitalization for fatal and nonfatal myocardial infarction and hospitalization for new-onset or worsening heart failure): (A) in patients with limiting angina at baseline; and (B) in patients with limiting angina and resting heart rate ≥70 bpm.

**Abbreviations:** BEAUTIFUL, morbidity-mortality Evaluation of the \( I_f \) inhibitor ivabradine in patients with coronary disease and left-ventricular dysfunction; bpm, beats per minute; CI, confidence interval; HR, hazard ratio.

Modified from reference 151: Fox et al. Eur Heart J. 2009;30:2337-2345. Published on behalf of the European Society of Cardiology. All rights reserved. © The Author 2009.

### SUMMARY

Pure heart rate slowing is very effective in preventing angina due to CAD. In addition, BEAUTIFUL strongly supports earlier data demonstrating the predictive value of heart rate as a risk marker in CAD. BEAUTIFUL also suggests, for the first time, that heart rate is a risk factor, the modification of which is likely to provide reduction in adverse outcomes over time in patients with chronic stable CAD and, particularly, for those with angina.

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Angina: Old Concepts Revisited

*Expert Answers to Three Key Questions*

1. Angina after revascularization: what is new?
   
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2. Myocardial ischemia as a multifactorial disease: what is new?
   
   M. Marzilli, A. Huqi, P. Capozza, D. Morrone

3. Angina and heart rate: what is new?
   
   J. C. Tardif, C. Y. W. Lee
Incethe advent of percutaneous coronary intervention (PCI) in 1977, the ability to mechanically dilate obstructive coronary artery stenoses has fundamentally altered our approach to managing patients with coronary artery disease (CAD). Over these decades, the remarkable and sustained evolution of this catheter-based technology has shifted treatment largely away from an initial pharmacologic approach to one that emphasized an anatomically-driven management strategy that has been particularly helpful in improving or alleviating angina symptoms that occur when flow-limiting coronary stenoses are successfully dilated. Importantly, over this same time period, significant advances have occurred in our understanding of the pathophysiologic basis for acute coronary syndromes (ACS) and the important role that plaque rupture or fissure plays in the genesis of acute myocardial infarction (MI), which clearly indicate that non-flow-limiting coronary stenoses are the principal progenitors of most “hard” clinical events. 1-3 We now recognize and fully embrace the premise that total or subtotal coronary occlusion following plaque rupture or fissuring is a cardiovascular emergency that cannot be optimally managed pharmacologically. Abundant trial data support the belief that urgent/emergent PCI in patients with ST-segment–elevation MI or high-risk non-ST-segment–elevation MI leads to a prognostically important reduction in death or subsequent MI. 4-9 Because performing PCI in patients with chronic angina and stable elective CAD is virtually identical pro-

Angina after revascularization: what is new?

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Over the past 35 years, myocardial revascularization, particularly percutaneous coronary intervention (PCI), has revolutionized the management of coronary artery disease (CAD) patients with acute coronary syndromes. However, compared with medical therapy, PCI does not reduce death or myocardial infarction in patients with chronic angina and stable CAD, although angina relief is universal. Recent optimal medical therapy (OMT) data appear to challenge older data suggesting the superiority of PCI for angina relief. More intensive secondary prevention and antianginal treatment may be increasingly effective in improving symptoms and quality of life. The substantial prevalence of angina postrevascularization (20%-45%) strongly suggests that even initially successful revascularization may not fully prevent the recurrence of symptoms. Although the benefits of OMT in chronic angina patients with stable CAD are clear, OMT rates remain disappointingly low in PCI patients.

Since the advent of percutaneous coronary intervention (PCI) in 1977, the ability to mechanically dilate obstructive coronary artery stenoses has fundamentally altered our approach to managing patients with coronary artery disease (CAD). Over these decades, the remarkable and sustained evolution of this catheter-based technology has shifted treatment largely away from an initial pharmacologic approach to one that emphasized an anatomically-driven management strategy that has been particularly helpful in improving or alleviating angina symptoms that occur when flow-limiting coronary stenoses are successfully dilated. Importantly, over this same time period, significant advances have occurred in our understanding of the pathophysiologic basis for acute coronary syndromes (ACS) and the important role that plaque rupture or fissure plays in the genesis of acute myocardial infarction (MI), which clearly indicate that non-flow-limiting coronary stenoses are the principal progenitors of most “hard” clinical events. 1-3 We now recognize and fully embrace the premise that total or subtotal coronary occlusion following plaque rupture or fissuring is a cardiovascular emergency that cannot be optimally managed pharmacologically. Abundant trial data support the belief that urgent/emergent PCI in patients with ST-segment–elevation MI or high-risk non-ST-segment–elevation MI leads to a prognostically important reduction in death or subsequent MI. 4-9 Because performing PCI in patients with chronic angina and stable elective CAD is virtually identical pro-

**SELECTED ABBREVIATIONS AND ACRONYMS**

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<tr>
<th>Abbreviation</th>
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<tr>
<td>ACS</td>
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<td>ARTS</td>
<td>Arterial Revascularization Therapy Study</td>
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<td>BARI-2D</td>
<td>Bypass Angioplasty Revascularization Investigation 2–Diabetes</td>
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<td>CABG</td>
<td>coronary artery bypass graft</td>
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<td>CAD</td>
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<td>COURAGE</td>
<td>Clinical Outcomes Utilizing Revascularization and Aggressive drUG Evaluation</td>
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<td>MI</td>
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<td>optimal medical therapy</td>
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cedurally to that performed in ACS patients, many have accepted the broader (but unproven) premise that PCI confers more durable clinical benefit (ie, improved survival, reduced rate of MI or hospitalization for ACS, and significant improvement in both angina and quality of life [QOL]) in this population of patients as well. Accordingly, the management of stable angina has been based largely on the “conventional wisdom” that the triad of angina, objective evidence of myocardial ischemia, and the presence of one or more flow-limiting coronary stenoses necessitated revascularization as the sine qua non of optimal treatment.

**PRINCIPAL CLINICAL OUTCOMES AND FINDINGS OF THE COURAGE TRIAL**

The Clinical Outcomes Utilizing Revascularization and Aggressive drugEvaluation (COURAGE) trial was designed to determine whether PCI coupled with optimal medical therapy (OMT) reduces the risk of death or nonfatal MI in patients with stable coronary artery disease (CAD), as compared with OMT alone.10,11 Such a robust “strategy trial” had never been conducted since the advent of angioplasty in 1977, although there were 11 prior studies that compared PCI in apposition to—not in combination with—OMT.12

COURAGE enrolled 2287 patients with objective evidence of myocardial ischemia and significant CAD from 50 US and Canadian centers. Between 1999 and 2004, 1149 patients were assigned to PCI with OMT and 1138 to OMT alone. The primary outcome was all-cause mortality or nonfatal MI during a 2.5- to 7.0-year (median 4.6 years) follow-up. Major clinical outcomes are summarized in Table I and Figure 1.11 There were 211 primary events in the PCI group and 202 events in the medical therapy group. The 4.6-year cumulative primary event rates were 19.0% and 18.5% in the PCI and medical therapy groups, respectively (hazard ratio [HR] in the PCI group compared with the medical therapy group, 1.05; 95% confidence interval [CI], 0.87 to 1.27; \( P =0.62 \)). Comparing PCI and medical therapy groups, there were no differences in death, MI, or stroke (20.0% vs 19.5%; HR, 1.05; 95% CI, 0.87 to 1.27; \( P =0.62 \)); hospitalization for acute coronary syndrome (12.4% vs 11.8%; HR, 1.07; 95% CI, 0.84 to 1.37; \( P =0.62 \)); or MI (13.2% vs 12.3%; HR, 1.13; 95% CI, 0.89 to 1.43; \( P =0.33 \)).11 Thus, the main study findings indicate that, as an initial management strategy in patients with stable CAD, PCI did not reduce death, MI, or other major cardiovascular events when added to OMT.
lief. Thus, there has been almost universal agreement that symptomatic improvement is superior with PCI as compared with medical therapy and, as a corollary, that recurrent angina requiring readmission and repeat PCI is uncommon after initially successful PCI.

ANGINA RELIEF AND IMPROVED QUALITY OF LIFE IN COURAGE

Rates of angina were consistently lower in COURAGE PCI patients as compared with the medical therapy patients during follow-up, and rates of subsequent revascularization were likewise lower. However, there was a substantial increase in freedom from angina in medically treated patients as well, most of which had taken place by 1 year, but with a further improvement to 5 years. To what extent this reflects a benefit of specific antianginal medications (such as nitrates and β-blockers) and to what extent it may reflect an effect of disease-modifying therapies, such as statins and inhibitors of the renin-angiotensin system, on coronary stenoses is unclear.

In addition, until the COURAGE trial was conducted it was largely unknown whether PCI could provide an incremental QOL benefit over OMT in patients with chronic angina due to stable CAD. A comprehensive, prospective assessment of QOL was imbedded in the trial proper during which angina-specific health status (Seattle Angina Questionnaire [SAQ]) and overall physical and mental function (RAND-36) were assessed at baseline and sequentially during follow-up. Clearly, how patients regard their own health and functioning is critical.

Figure 1. Kaplan-Meier survival curves.
In Panel A, the estimated 4.6-year rate of the composite primary outcome of death from any cause and nonfatal myocardial infarction was 19.0% in the PCI group and 18.5% in the medical-therapy group. In Panel B, the estimated 4.6-year rate of death from any cause was 7.6% in the PCI group and 8.3% in the medical-therapy group. In Panel C, the estimated 4.6-year rate of hospitalization for acute coronary syndrome (ACS) was 12.4% in the PCI group and 11.8% in the medical-therapy group. In Panel D, the estimated 4.6-year rate of acute myocardial infarction was 13.2% in the PCI group and 12.3% in the medical-therapy group.

Abbreviations: ACS, acute coronary syndrome; PCI, percutaneous coronary intervention.
and both the SAQ and RAND-36 are patient-reported health outcome instruments.

Based on the SAQ analysis, there was significantly better angina control with PCI for the first 12-24 months across the key domains of physical limitation, anginal frequency, and QOL. While the differences between treatment arms were statistically significant, the clinical differences were substantially smaller than the within-group benefits noted for both arms. The SAQ data were likewise supported by the RAND-36, which, as a general health questionnaire, showed less consistent benefit of PCI+OMT because not all scales on the RAND-36 showed incremental benefit of PCI+OMT. Somewhat unexpectedly, there was rapid improvement in health status for almost all measures in both groups by 1- to 3-month follow-up. Importantly, there was significant and rapid improvement in SAQ scores in OMT patients who did not cross over to PCI+OMT. However, the small group of patients who crossed over early from OMT to PCI+OMT (only 16.5% of OMT patients crossed over during the first year of follow-up) had remarkably low SAQ scores at baseline, and rapid and dramatic improvement in their scores.\(^{15}\)

What this indicates is as follows: COURAGE demonstrated that an initial strategy of PCI added to OMT relieved angina to a greater extent than an initial strategy of OMT alone for a period of approximately 24 months. Since the overall COURAGE trial results did not show that the addition of PCI to OMT reduced cardiovascular events,\(^{10,11}\) these important QOL findings\(^{15}\) permit physicians to engage in an evidence-based discussion with patients about the expected clinical and health status benefits of initial versus deferred PCI when added to OMT. If PCI is deferred, physician and patient alike can be confident that risk of MI or death is not increased. This should foster a patient-centered approach that considers both the incidence of clinical events as well as health-related QOL to help guide the decision about timing and the need for PCI.

**EFFECT OF PCI ON ANGINA RELIEF: A SYSTEMATIC ANALYSIS**

PCI is prominent in the treatment of patients with stable CAD. More than half of all PCIs (approximately 600 000 annually) are done for this indication each year in the United States.\(^{16}\) Several meta-analyses have compared the efficacy of PCI versus medical therapy in patients with stable CAD; however, these analyses have focused on death, MI, and repeated coronary revascularization and have consistently demonstrated no incremental benefit of PCI compared with medical therapy.\(^{17-19}\)

Although relief of angina may be the most appropriate indication for PCI among patients with stable CAD in contemporary interventional practice, until recently no systematic review had estimated the efficacy of PCI for angina relief compared with medical therapy. Although evidence from early randomized trials has shown that PCI provides substantial angina relief compared with medical therapy, more recently published trials have challenged this conventional wisdom.\(^{20-23}\) For example, in the RITA-2 (Randomized Intervention Treatment of Angina-2) trial, investigators found that PCI patients were almost twice as likely to not have angina at 3 years.\(^{21,23}\) By contrast, in the COURAGE trial, only a small, early incremental benefit associated with PCI for angina relief was demonstrated, compared with OMT.\(^{11}\)

These discrepancies underscore the need to systematically evaluate the efficacy of PCI versus medical therapy for long-term angina relief.\(^{24}\) Accordingly, Wijeyasurya and co-workers\(^{25}\) performed a systematic review of the literature to best estimate the degree of angina relief associated with PCI compared with medical therapy in patients with stable CAD.

They used prespecified subgroup analysis and meta-regression techniques and evaluated several key study-level factors that might have contributed to heterogeneity across trials, such as the length of follow-up, inclusion of patients with recent acute MI, use of coronary stents, recruitment period, and use of evidence-based therapies.

The authors identified relevant published studies through a computerized literature search of the Cochrane Library (1993 to June 2009), EMBASE (1980 to June 2009), and MEDLINE (1950 to June 2009) electronic databases using the terms “transluminal percutaneous coronary angioplasty” and “angina pectoris.” Inclusion criteria included randomized trials that enrolled patients with stable CAD and compared a treatment strategy of PCI versus medical therapy. Because no universally acceptable definition of when a patient with unstable CAD becomes stable exists, they included trials that enrolled patients with recent acute coronary syndromes that had been stabilized for more than 1 week.

Of the 14 trials that comprised the meta-analysis, most included patients who were men with normal left ventricular systolic function. The proportion of patients with diabetes mellitus ranged from 9% in the RITA-2 trial to 33% in the COURAGE trial. 57.5% had single-vessel dis-
ease, 28.8% had double-vessel disease, and 13.6% had triple-vessel disease. Six trials, with 3010 patients, restricted enrollment to patients who had been stabilized after acute MI.

There were no substantial differences in baseline utilization rates for evidence-based medications among trials. Although aspirin was used frequently in all studies, with rates ranging from 75% to 100%, use of other medications varied widely among the trials. For example, angiotensin-converting enzyme inhibitor use ranged from 8% to 80%, whereas statin use ranged from 12% to almost 90% in more recent trials. Rates of medication use were similar between patients randomly assigned to PCI versus those assigned medical therapy within each trial, with rare exceptions.

**FREEDOM FROM ANGINA IN THE META-ANALYSIS**

Overall, PCI was associated with improvement in freedom from angina compared with medical therapy (summary odds ratio |OR|, 1.69; 95% CI, 1.24 to 2.30; \( P = 0.001 \)). At the end of trial follow-up, 73% of PCI patients were angina-free, compared with 64% of patients who received medical therapy alone (number need to treat, 10 [CI, 6 to 29]; \( P = 0.003 \)). However, significant heterogeneity across studies was observed (\( P = 0.001 \)), with an I2 statistic of 73%, indicating marked variation in the estimates of freedom from angina for PCI versus medical therapy across studies (Figure 2).

The effect of PCI on freedom from angina on the basis of the length of follow-up in the studies was assessed. PCI was associated with significant angina relief among trials with less than 1-year follow-up (71.4% of PCI patients vs 64.3% of patients who received medical treatment were angina-free) and also among trials with 1- to 5-year follow-up (71.3% vs 61.9%). Among the 5 trials with more than 5-year follow-up, however, the incremental benefit of PCI versus medical therapy did not achieve statistical significance (Figure 3, page 184).

**META-REGRESSION OF FREEDOM FROM ANGINA AND MEDICAL THERAPY**

Figure 3 also shows the meta-regression analysis plotting the treatment effects of PCI relative to medical therapy versus utilization of evidence-based medications. A statistically significant inverse relation-
ship was observed between freedom from angina and number of evidence-based medications used in a trial ($P=0.021$).

In more contemporary trials in which evidence-based medications were used more often, the benefit associated with PCI for symptom relief was diminished. On average, with each additional medication class, the advantage of PCI over medical therapy for angina relief decreased by 31% (CI, 14% to 45%). This finding remained consistent when the threshold for defining medication use in a trial was varied from 30% to 70%. In addition, a meta-regression analysis pooling utilization rates of medical therapy from each trial was performed and revealed a similar significant inverse relationship between medical therapy and PCI. Thus, although the results of this meta-analysis demonstrated that PCI (when added to medical therapy) was associated with an overall improvement in angina relief for patients with stable CAD compared with medical therapy alone, the incremental benefit of PCI on angina relief diverged substantially across the trial periods included in this meta-analysis. In fact, angina relief benefit associated with PCI was predominantly restricted to older trials, with contemporary studies showing no significant differences between patients who received treatment with PCI and more intensive, multifaceted OMT.

One key reason might be improvement in the proportion of patients who received contemporary “optimal” medical treatment and became angina-free over time, from 40% in older trials, to 57% in intermediate trials, and to 75% in contemporary trials. The increasing proportion of patients who were angina-free corresponded to an increasing use of evidence-based medical therapy among trials. There was an inverse relationship between use of evidence-based therapies and efficacy of PCI in the meta-regression analysis. These findings were robust in several sensitivity analyses and were not overly influenced by any single trial, such as COURAGE. These findings, which suggest that important improvements in OMT might explain the attenuated effect of PCI on angina relief in contemporary practice, highlight the degree to which OMT has “leveled the playing field” in more recent trials where angina relief following PCI vs medical therapy has been critically assessed as an outcome of interest.
ANGINA FOLLOWING REvascularization

A prevalent belief among many interventionalists and cardiac surgeons is that postrevascularization angina is uncommon, given the short-term effectiveness of alleviating the symptom-producing flow-limiting stenoses that are encountered in both patients with ACS and stable CAD. A more rigorous assessment of the prevalence of recurrent angina following initially successful revascularization from observational registries, administrative databases, and randomized clinical trials reveals that rates of recurrent angina are appreciable, and frequently result in repeat hospital admissions and repeat revascularization procedures, especially PCI. Data from the National, Heart, Lung, and Blood Institute’s Dynamic PCI Registry showed a 1-year recurrence rate of post-PCI angina of 26% among 1755 patients who initially underwent successful PCI for CAD. In addition, at 1-year of follow-up, 61% of patients still received a β-blocker and 79% of patients required one or more antianginal agents.

In a retrospective cohort analysis of Medicare fee-for-service admissions associated with PCI in 2005, Curtis and coworkers sought to examine the rates of all-cause readmission and repeat revascularization within 30 days after an initially successful PCI. A total of 315,241 PCI procedures performed at 1108 hospitals were included in the analysis. The all-cause 30-day readmission rate was 14.6%, and the all-cause 30-day mortality rate was 1.0%. All-cause 30-day mortality among readmitted patients was higher than patients who were not readmitted (3.6% vs 0.6%; P < 0.001). The 30-day readmission rate of acute MI patients was significantly higher than that of non-MI patients (MI 18%, non-MI 14%, P < 0.001). Among all patients readmitted within 30 days after index PCI, 28% had an associated revascularization procedure (PCI, 26%, coronary artery bypass graft [CABG], 1.7%). The median readmission rates varied across hospitals, from 8.9% in the lowest decile to 22.0% in the highest decile. From these results, the authors concluded that a substantial proportion of PCI patients are readmitted within 30 days of discharge and that readmission rates varied widely across hospitals. Readmissions within 30 days of an index PCI procedure were associated with a significantly higher 30-day mortality rate, and more than a quarter of such readmissions resulted in a repeat revascularization procedure. In addition, data from numerous randomized controlled trials of PCI vs CABG surgery and of PCI vs medical therapy offer important, additional insights into the frequency of postrevascularization angina.

In the previously published ARTS (Arterial Revascularization Therapy Study) trial, which compared clinical outcomes among 1205 patients who were randomized to bare-metal stent PCI or CABG surgery, the rate of recurrent angina at 1-year of follow-up was 21% in the stented group as compared with 11% in the surgery group, while the need for continued antianginal medication was 79% in the stented patients as compared with 59% in the CABG-treated patients. Overall, 81% of PCI-treated patients and 62% of surgically-treated patients displayed either continued angina and/or required antianginal medication at 1-year of follow-up.

In the aforementioned COURAGE trial, 34% of patients displayed recurrent or persistent angina at 1-year of follow-up among those randomized to PCI, although the rate of recurrent angina was significantly higher in the medically-treated patients (42%). At 3 and 5 years of follow-up, among COURAGE trial patients randomized to PCI, rates of recurrent or persistent angina were 27% and 26%, respectively. Additionally, at 1 year of follow-up among patients originally assigned to PCI, 10.5% required a second revascularization procedure. In the SYNTAX (SYnergy between percutaneous coronary intervention with TAXus and cardiac surgery) trial, where 1800 patients with 3-vessel and/or left main stem CAD were randomized to receive drug-eluting stents (Taxus) or CABG surgery, 28% of PCI-treated patients had recurrent angina at 1-year of follow-up. For comparison, in the 1434 patients who had “classic angina” at baseline out of the 2368 CAD patients with type 2 diabetes mellitus in the BARI-2D (Bypass Angioplasty Revascularization Investigation 2–Diabetes) trial, 60% exhibited recurrent angina at 1-year of follow-up in the setting of comorbid diabetes. The data for the five studies cited above are illustrated in Figure 4 (page 186).

Lastly, in an administrative claims database of CAD patients from a large health-maintenance organization, among 18,420 patients who underwent an initial PCI revascularization procedure, 8420 (46%) developed recurrent angina for which ≥2 nitrate prescriptions had been prescribed within 1 year of follow-up. Of these, 2904 patients (35% of recurrent angina patients) required a second revascularization procedure at 1 year. The mean time to the second revascularization procedure, after the diagnosis of recurrent angina, in this database was 73 ± 103 days.

Thus, data derived from a variety of sources (observational registries, randomized controlled trials, and
administrative claims databases) suggest strongly that rates of recurrent angina in stable CAD patients may range from roughly 20% to 45% among patients who undergo initially successful revascularization with PCI. Presumably, the recurrence of angina is multifactorial, and may be attributed to restenosis or disease progression in initially non-instrumented coronary arteries.

**CLINICAL PRACTICE IMPLICATIONS**

Why is it, then, that PCI reduces death or MI in ACS patients, but does not apparently confer the same cardioprotective effects in chronic angina patients with stable CAD patients? After all, stable CAD patients in both COURAGE and BARI-2D exhibited significant myocardial ischemia and extensive multivessel CAD for which one might have anticipated a more durable clinical benefit of PCI over and above mere angina relief. Our findings may be explained, in part, by differences in atherosclerotic plaque morphology and vascular remodeling associated with ACS as compared with stable CAD.

Vulnerable plaques, precursors of ACS, tend to have thin fibrous caps, large lipid cores, fewer smooth muscle cells, more macrophages, less collagen, and are associated with outward (expansive) remodeling of the coronary artery wall, causing less stenosis of the coronary lumen. As a result, vulnerable plaques do not usually cause a significant stenosis prior to rupture and precipitation of an acute coronary syndrome. By contrast, stable plaques tend to have thick fibrous caps, small lipid cores, more smooth muscle cells, fewer macrophages, more collagen, and are ultimately associated with inward (constrictive) remodeling that narrows the coronary lumen.

These lesions produce ischemia and anginal symptoms, are easily detected by coronary angiography, but are less likely to result in an acute coronary syndrome. Focal management of even severely stenotic coronary lesions with PCI in COURAGE and BARI-2D did not reduce death or MI, presumably because these treated stenoses were not likely to trigger an ACS event. Furthermore, our lower than projected event rate in the medical therapy group may be explained by systemic therapy that reduced plaque vulnerability through aggressive, multiple-risk-factor intervention and evidence-based medication use.

As noted above, one of the prevalent beliefs in patients with stable CAD who undergo PCI is that despite the absence of a definable clinical benefit of “hard end point” (eg, death and/or MI) reduction, PCI is superior to medical therapy for the end point of angina relief.

Another is that recurrent angina following initially successful PCI is uncommon in the setting of contemporary catheter-based intervention. While numerous early comparative studies of PCI vs medical therapy show a strong treatment benefit in angina relief with PCI (meta-analysis of 14 trials show a relative risk reduction of 69% as compared with medical therapy), more recent trials employing intensive, multifaceted medical therapy with longer periods of follow-up show that this treatment superiority of PCI over “optimal” medical therapy is largely abolished. Such clinical outcome data provide mounting evidence that OMT has, in many respects, “leveled the playing field” as compared with initial PCI for angina relief, although clearly during short-term follow-up, PCI still remains superior to medical therapy.
for improvements in both angina relief and QOL over the initial 1-2 years of follow-up. For these reasons, where patients remain symptomatic despite medical therapy, or when medical therapy fails to improve OOL or symptoms, PCI is a safe and proven approach to improve angina and return patients to a more normal functional capacity.

Lastly, we continue to be challenged by the recurrence (or persistence) of angina following initially successful revascularization, especially in PCI-treated patients. While clearly the use of drug-eluting stents has significantly reduced rates of restenosis of the target lesion or target vessel, many patients with extensive, multivessel CAD and multiple risk factors for CAD progression that remain incompletely treated medically are at higher risk for developing anginal symptoms emanating from coronary stenoses involving different vascular beds than those intervened upon during the index PCI procedure.

Unfortunately, our own clinical practice guidelines fail to define the appropriate intensity of anti-ischemic medical therapy. In one study of patients with chronic stable angina who were referred for coronary angiography, intensity averaged only 15 on a scale from 0 to 100—equivalent to an average dose of a single antianginal drug—and 15% were not being treated with any antianginal medications. These findings have important implications regarding the management of patients with angina and stable CAD and the associated national costs of health care. Quite simply, the erroneous conclusion may be that medical therapy fails in a large number of patients when, in fact, those patients never received enough medical therapy to make that determination.

Moreover, recent data from Borden and coworkers, published in the *Journal of the American Medical Association* in May 2011, examine the use of OMT before and after PCI and to evaluate whether the use of OMT changed after the publication of the COURAGE trial. The study included data from the National Cardiovascular Data Registry of patients with stable CAD undergoing PCI between September 2005 and June 2009. Analysis compared use of OMT, both before PCI and at the time of discharge, and before and after the publication of the COURAGE trial. OMT was defined as being prescribed unless patients had a documented contraindication to all medicines (antiplatelet agents, β-blockers, and statins).

Despite guideline-based recommendations that underscore the importance of OMT for patients with stable coronary heart disease undergoing PCI, data derived from this large cardiovascular registry indicated that less than half of eligible patients are receiving OMT before PCI and approximately one third are not receiving OMT at discharge following PCI. A total of 467,211 patients undergoing PCI were included in the analysis, with 173,416 patients (37%) and 293,795 patients (63%) in the before and after COURAGE periods, respectively.

The researchers found that 206,569 patients (44%) received OMT before PCI and 303,864 patients (65%) received OMT at the time of discharge. Thus, before the COURAGE trial, the rate of OMT at the time of PCI was 43.5%. Although the increase in the proportion of patients receiving OMT before PCI after the COURAGE trial was statistically significantly higher, it was of little clinical significance (131,188 patients [44.7%]). The rates of OMT before PCI in each study period month showed a small increase during the 46 months of observation, with an OMT rate before PCI of 43.4% in September 2005 and an OMT rate after PCI of 45% in June 2009. The overall rate of OMT after PCI, a time at which the diagnosis of significant obstructive CAD had been confirmed, was 64% before the COURAGE trial and 66% after the COURAGE trial.

These important results underscore the fact that less than half of patients undergoing PCI are taking OMT before their procedure, despite the guideline-based recommendations to maximize OMT, and the clinical logic of doing so, before PCI so that the need for additional symptom relief from revascularization can be appreciated. Even after publication of the COURAGE trial, little change in this practice pattern has been observed. Although clinicians did increase the use of OMT before discharge, with antiplatelet agents being almost universally applied, almost a third of patients were not treated with OMT, a pattern that did not change after the COURAGE trial was published. Collectively, these findings suggest a significant opportunity for quality improvement and achieving a higher level of best practice.

**CONCLUSION**

Simply stated, CAD is a systemic problem that requires systemic treatment. Flow-limiting lesions cause angina and ischemia, but they may not necessarily be the lesions predisposing to death, MI, and ACS. OMT is directed toward stabilizing so-called vulnerable plaques that are frequently mild angiographically and nonobstructive, such that OMT should rightfully be regarded as the preferred therapeutic approach to reducing clinical events in patients with chronic coronary syndromes.
and as a complementary approach to focal revascularization methods directed toward angina and ischemia relief, if needed. Achieving and maintaining multiple treatment targets may be a difficult challenge, but is well worth the effort.

In addition, in order to favorably impact rates of recurrent or persistent angina postrevascularization, clinicians need to be ever mindful that it is essential to aggressively treat predisposing risk factors with proven secondary prevention therapeutic interventions and to treat recurrent angina with both traditional antianginal agents (eg, β-blockers, calcium antagonists, long-acting nitrates, etc) and, if needed, to consider more novel agents, such as ranolazine, ivabradine, or nico-randil. Only then will we be able to achieve the highest levels of symptomatic improvement, and the likelihood of enhancing event-free survival for our patients.

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Myocardial ischemia as a multifactorial disease: what is new?

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Strategies for ischemic heart disease (IHD) focus almost exclusively on coronary atherosclerosis because access to interventional procedures is easy and gives gratifying angiographic results. This assumes that coronary artery disease and IHD are functionally identical. Recent reports, however, challenge the “plaque-centric” hypothesis of IHD. Alternative mechanisms, including coronary microvascular dysfunction, endothelial dysfunction, platelet dysfunction, coronary vasospasm, and inflammation, can precipitate myocardial ischemia (MI) in man. So, to assume that stenosis removal is a consistent cure for IHD is unwise, as is discounting MI because an angiogram appears “normal” after percutaneous coronary intervention or assuming MI is present because an atherosclerotic plaque is visible on angiography.

Back in 1974, Gould et al described the effects of coronary artery narrowing on resting and maximal coronary blood flow. Such findings gained widespread acceptance and generated a lot of excitement about subsequent studies that assessed the feasibility of local coronary stenosis removal. In fact, as early as 1976, Gruentzig presented the results of animal studies of coronary angioplasty at an international cardiology meeting, which were quickly followed (in 1977) by the first in-human coronary balloon angioplasty, performed intraoperatively. Only a year later the same author performed the first percutaneous transluminal coronary angioplasty on a conscious patient in Zurich, marking in this way the historical passage of cardiology from a drug-oriented discipline to a hybrid discipline featuring internal medicine and surgery. The advent of interventional cardiology has undoubtedly changed the management of patients with coronary artery disease (CAD), and the progressive evolution in techniques and new devices has permitted the extension of indications to both chronic and acute conditions. Moreover, patients with CAD who, because of increased intraoperative risk, are not be eligible for revascularization with coronary artery bypass grafting (CABG), have also benefited from this therapeutic option. For all these reasons, percutaneous coronary interventions (PCI) constitute one of the most frequently performed medical interventions, with more than 2 million procedures per annum worldwide.

However, despite the gratifying progress, neither the advent of PCI itself nor the progressive sophistication of percutaneous techniques has changed the natural history (in terms of death or myocardial infarction) of CAD patients, when compared with medical therapy. Moreover, following coronary revascularization, large clinical trials have persistently reported that many angina patients present...
with persistent symptoms. However, as these studies were designed for investigating other end points, the incomplete benefits of PCI have usually been discounted and attributed to a combination of procedure-related factors (i.e., restenosis, incomplete revascularization, etc) and patient-related factors (i.e., left ventricular hypertrophy, valvular disease, etc). In addition, the few studies that have assessed patients with persistent angina, by means of stress testing, have shown a particularly high rate of positive results, more often than not followed by the need for repeat revascularization (i.e., patent coronary artery).11-13 As a consequence, although not properly defined, the use of routine stress testing in the first 2 years after PCI and 5 years after CABG has been strongly discouraged.14-16

**LIMITS OF REvascularization IN CHRONIC ISCHEMIA**

To investigate in more depth the need for repeat revascularization in CAD patients, we conducted a study on a highly select chronic angina patient population17 undergoing PCI, which we tried to control for confounding factors to the best of our ability. Only patients with stable angina and a positive exercise stress test, who had undergone a complete (no residual stenosis of ≥10% in any vessel of ≥2 mm in diameter) and uncomplicated revascularization procedure, were included. To facilitate electrocardiogram interpretation, we excluded patients with congestive heart failure, left ventricular hypertrophy, bundle-branch block, valvular heart disease, previous myocardial infarction, and complete chronic coronary occlusions, and those on digoxin. Exercise tolerance and quality of life in 220 patients were assessed with an exercise stress test and the Seattle Angina Questionnaire (SAQ), respectively. Patients were evaluated at baseline and after 1 month, to minimize the interference of restenosis. Patients were also reassessed at 6 and 12 months after index PCI. At baseline, per protocol all patients had positive exercise stress test results and a moderately impaired quality of life as assessed by SAQ. One month after the “successful” PCI, 50% of patients still had a positive stress test (Figure 1).15 Similar rates of positive exercise stress test results were obtained at the 6- and 12-month follow-up visits.

Most importantly, one third of the population admitted to still being symptomatic for angina and reported an unsatisfactory quality of life, as assessed by SAQ. Consistent with previous studies,18-22 coronary angiography documented in-stent restenosis in less than 10% of patients. Although not designed to provide pathophysiological insights, this study may give a clue to helping understand the lack of categorical benefit from revascularization observed in recently published large clinical trials. Put simply, patients who do not improve after a “successful” revascularization procedure may have alternative mechanisms that are responsible for their symptoms, and these alternative mechanisms are unmasked by stenosis removal.

**OTHER CAUSES OF CHRONIC ISCHEMIA**

Obstructive CAD as a cause of reduced coronary blood flow reserve has been widely validated in both experimental models23 and clinical settings. However, in contrast with the linear model originally proposed by Gould et al,23 the close relationship between stenosis severity and coronary flow reserve described in anaesthetized, open chest, healthy dogs, becomes much more elusive when transferred to the clinical setting.24,25 In man, as in experimental animals, angina and myocardial ischemia are expected to be caused by a flow-limiting stenosis in a large epicardial coronary artery. However,
this assumption is not always true when tested in the individual patients. Conversely, angina and myocardial ischemia are frequently observed in the absence of any visible stenosis. For example, a clinical condition, known as “syndrome X,” is characterized by effort angina and positive exercise stress test in patients with a normal coronary angiogram. This condition has been attributed to reduced coronary blood flow due to increased microvascular resistance. At the other end of the spectrum, many investigators have observed an abnormally low coronary flow reserve following angioplasty and stenting, in one third of patients. However, assessment of coronary microvascular function is difficult to monitor on a routine basis because it is technically demanding, invasive, and expensive and also because to date there are no interventions that can potentially “fix” any abnormality found. That’s why, in common practice, microvascular dysfunction is only considered as a possible cause of ischemia in IHD when obstructive CAD is not present.

In acute coronary syndromes (ACS), it is widely accepted that rupture and/or erosion of a “vulnerable” atherosclerotic plaque may trigger thrombus formation and abrupt vessel closure. When no atherosclerotic lesion is visible on coronary angiography, coronary spasm has been proposed as an alternative cause. In this regard, recently published large clinical trials have shown that this phenomenon is not as infrequent as previously thought, in that more than 30% of ACS patients do not present with a “culprit lesion” on coronary angiography. When systematically tested by intracoronary administration of acetylcholine, coronary vasospasm is documented in 50% of cases, implying that coronary smooth muscle dysfunction may be a trigger for an acute ischemic event. Indeed, coronary vasospasm has often been associated with progression of atherosclerotic disease. However, as with chronic IHD, alternatives to CAD are only investigated when a “logical” explanation to an event is lacking.

To verify this assumption, we recently performed a study to assess the presence and prevalence of active vasospastic constriction in patients presenting with a non-ST-segment–elevation myocardial infarction (NSTEMI) at the site of the culprit lesion. Twenty-five consecutive patients with NSTEMI and an atherosclerotic obstruction of the culprit vessel were included. Stenosis severity was assessed by quantitative coronary angiography (QCA) and fractional flow reserve (FFR). At baseline, all patients presented with a tight coronary stenosis (QCA showing >75% diameter reduction) and severe flow obstruction (FFR <0.75). Following intracoronary administration of nitrates, there was an immediate and significant decrease of QCA-assessed stenosis severity in all patients and, in 18 patients (72%), FFR normalized. These data are consistent with the hypothesis that active coronary vasospastic constriction contributes to stenosis severity and flow obstruction at the level of the culprit lesion in NSTEMI patients, and may therefore precipitate an acute ischemic event.

**CONCLUSION**

Most cardiologists are well aware that a number of mechanisms may be responsible for myocardial ischemia in man. Nevertheless, preventive and therapeutic strategies focus almost exclusively on coronary atherosclerosis, assuming that CAD and IHD are functionally identical. This approach has produced a progressive rise in the number of revascularization procedures per-
formed worldwide and has inflated the costs to levels that few countries can afford. Numerous observations—the limited impact of this approach on prognosis (if any), the persistence of symptoms in patients in whom CAD has been removed, the noting of dynamic changes in culprit lesion severity, etc.—strongly challenge this “plaque-centric” approach to IHD. A number of additional mechanisms have long been known to precipitate myocardial ischemia in man, including coronary microvascular dysfunction, endothelial dysfunction, platelet dysfunction, coronary vasospasm, and inflammation. These mechanisms, which can operate in isolation or in combination, can occur in the presence or in the absence of visible coronary atherosclerosis. It is no longer tenable to discount the presence of myocardial ischemia just because an angiogram appears “normal” after PCI or to assume myocardial ischemia is present just because an atherosclerotic plaque is visible on angiography.\textsuperscript{41,44}

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Angina and heart rate: what is new?

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Ivabradine, a novel antianginal drug that solely reduces heart rate (HR), represents an important medical advance in the treatment of angina. Selective If inhibition with ivabradine prolongs slow diastolic depolarization in the sinus node, without affecting the action potential. Ivabradine reduces HR in a dose-dependent manner, lowering the metabolic demand of the heart and enhancing coronary perfusion during diastole, without altering standard cardiac parameters. It is also safe and well tolerated. Ivabradine has no significant effects on myocardial contractility or other hemodynamic parameters, nor does it significantly affect ventricular repolarization or other electrophysiological parameters. Furthermore, neither glucose metabolism nor respiratory function is impaired. This article reviews several key ivabradine studies and the use of ivabradine, whether as monotherapy or in combination with β-blockers, in chronic stable angina.

Keywords: angina; heart rate; ivabradine

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Angina and heart rate: what is new? - Tardif and Lee

**HEART RATE AS A CARDIOVASCULAR RISK FACTOR**

Multiple epidemiological studies have demonstrated that a higher resting HR is a predictor of morbidity, as well as cardiovascular (CV) and all-cause mortality. Moreover, the value of this readily measurable clinical parameter as an independent predictor of CV events and death has been demonstrated in both men and women. Increased HR is associated with elevated CV risks both in healthy individuals and in those with CV diseases. Moreover, increased resting HR over time predisposes individuals to the development of vascular disease and is an independent risk factor in patients with coronary artery disease (CAD), MI, and hypertension.

From a pathophysiological point of view, a higher HR increases myocardial oxygen demand and decreases oxygen supply (the latter via reduced myocardial perfusion as a consequence of shortening of diastole, during which most myocardial perfusion occurs), leading to myocardial ischemia. Moreover, in the presence of CAD, an elevated HR may result in “collateral steal,” a phenomenon whereby blood flow is redistributed away from ischemic myocardium and toward normal myocardium owing to impaired vasodilation in diseased coronary vessels, as opposed to normal vasodilation with augmented blood flow. Similarly, redistribution of blood flow away from the subendocardium toward the epicardium may occur, due to increased susceptibility of subendocardial vessels to developing compromised vasodilator function in the setting of ischemia. With CAD, acute elevations in HR may result in paradoxical vasoconstriction in diseased epicardial coronary arteries and the associated microvasculature. The formation of collateral vessels may also be impaired, further predisposing vulnerable myocardium to ischemic insults.

Chronic exposure to altered shear stress secondary to elevated HR contributes to the pathogenesis of vascular lesions. Increased HR is associated with endothelial dysfunction, accelerated atherosclerosis progression, and an augmented risk of plaque rupture in the coronary arteries (Figure 1, page 198). Moreover, an elevated HR predisposes large arteries to increased cyclical stretch, resulting in functional deterioration of elastin fibers, increased vascular stiffness, and augmentation in left ventricular (LV) afterload, which may eventually culminate in the development of LV hypertrophy and fibrosis. The latter may in turn lead to reduced coronary flow reserve with consequent myocardial ischemia, diastolic dysfunction, ventricular arrhythmias, and sudden cardiac death.

**PHARMACOLOGY OF IVABRADINE**

Ivabradine, \[3-(3-\{1\{7\}S\}3,4-dime-thoxybicyclo[4,2,0]octa-1,3,5-trien-7-yl)-methyl\]methylamino\]propyl]-1,3,4,5-tetrahydro-7,8-dimethoxy-2H-3-benzazepin-2-one], is a pure HR-lowering drug that selectively inhibits the pacemaker hyperpolarization-activated current, \(I_t\) or \(I_{f}\). Selective \(I_t\) inhibition with ivabradine prolongs slow diastolic depolarization in the sinus node without affecting the characteristics of the action potential. Ivabradine reduces HR in a dose-dependent manner, thereby lowering the metabolic demand of the heart and enhancing coronary perfusion during diastole (which lengthens with HR lowering), without altering 

Following oral administration, ivabradine is rapidly absorbed with the maximum plasma concentration being reached within an hour. It is approximately 70% protein-bound and has a short half-life and the effective half-life of ivabradine are 2 and 11 hours, respectively. Metabolic clearance constitutes 80% of the total clearance of ivabradine, with the other 20% being renal clearance. Approximately 4% of an oral dose is excreted unchanged in urine.
Based on multiple experimental and clinical studies, it has been well documented that inhibition with pure HR reduction, with subsequent lowering of myocardial oxygen demand and increased diastolic coronary perfusion, constitutes the fundamental mechanism of benefit of ivabradine in CAD.\textsuperscript{38,39} In addition, emerging mechanisms of benefits, as demonstrated mostly in experimental studies to date, also include: improvement in endothelial function or prevention of endothelial dysfunction\textsuperscript{40-42}; inhibition of chemokine-induced migration of CD4-positive lymphocytes (a key step in atherogenesis) and reduction in plaque formation\textsuperscript{43}; attenuation of oxidative stress\textsuperscript{40}; reduction in perivascular collagen and enhancement in maximal myocardial perfusion and coronary reserve\textsuperscript{44}; attenuation of myocardial fibrosis\textsuperscript{45}; favorable effects on systolic and/or diastolic function\textsuperscript{45,46}; and lowering of angiotensin II and aldosterone levels (and their associated adverse CV effects)\textsuperscript{45}; antiremodeling postinfarction\textsuperscript{47}; enhanced vascularity\textsuperscript{48}; and attenuation of myocardial ischemia-reperfusion injuries\textsuperscript{49-51}. The latter may involve an increase in the threshold for ischemia-induced ventricular fibrillation and preservation of the ultrastructure of the mitochondria\textsuperscript{49-51}. Moreover, ivabradine reduces oxidative stress and fibrosis, resulting in improvements in endothelial function\textsuperscript{52}. In a murine model of cerebral ischemia, ivabradine improved endothelial function in the cerebral vasculature, attenuated oxidative stress, and reduced infarct volume\textsuperscript{42}. The major mechanisms are summarized in Table 1.
EARLY CLINICAL TRIAL DATA ON IVABRADINE

In the first large double-blind, placebo-controlled, multicenter clinical trial of ivabradine, Borer et al.\(^{53}\) randomized 360 patients with chronic stable angina to receive placebo or ivabradine 2.5, 5, or 10 mg bid for 2 weeks, which was followed by an open-label extension on ivabradine 10 mg bid for 2 or 3 months and a 1-week randomized withdrawal phase. Using time to 1-mm ST-segment depression and time to limiting angina during bicycle exercise tolerance tests (ETTs), performed at trough of drug activity, as the primary efficacy end points, the investigators demonstrated the safety of the 3-month course of ivabradine therapy, as well as dose-dependent improvements in exercise tolerance and time to the development of ischemia.\(^{53}\) In subsequent clinical trials, ivabradine was demonstrated to have similar anti-ischemic and antianginal efficacy compared with \(\beta\)-blockers and calcium channel blockers (CCB) as discussed below.\(^{31}\)

**Comparison with \(\beta\)-blockers**

In the double-blinded INITIATIVE trial (INternational TRIAl on the Treatment of angina with IVabradinE versus atenolol) involving 144 centers in 21 countries, Tardif et al.\(^{54}\) randomized 939 patients with stable angina to ivabradine (5 mg twice a day for 4 weeks, then 7.5 or 10 mg twice a day for 12 weeks) or atenolol (50 mg daily for 4 weeks, then 100 mg daily for 12 weeks) to compare the antianginal and anti-ischemic effects of the two drugs in patients with stable angina. Treadmill exercise tests were performed at randomization and after 4 and 16 weeks of therapy. The primary efficacy end point was total exercise duration during treadmill tests from inclusion to the end of the 16-week treatment, assessed at trough of drug activity. Secondary efficacy criteria were changes in time to limiting angina, time to angina onset, ST-segment depression, HR, rate pressure product, total exercise duration, and other treadmill criteria at peak drug activity; selected criteria from inclusion to the end of 4 weeks; and frequencies of angina and short-acting nitrate use. These investigators demonstrated the noninferiority of ivabradine versus atenolol at all doses evaluated and for all criteria.\(^{54}\) A two-thirds reduction in angina episodes was observed in both groups.\(^{54}\)

**Comparison with calcium channel blockers**

Ruzyllo et al.\(^{55}\) conducted a randomized, double-blind, multicenter noninferiority trial to evaluate the antianginal efficacy and safety of ivabradine versus the dihydropyridine CCB amlodipine in patients with stable effort-induced angina. HR was significantly reduced both at rest and with bicycle exercise by ivabradine only. Ivabradine (7.5 mg and 10 mg daily) exhibited comparable efficacy to amlodipine (10 mg daily) in improving exercise tolerance. Moreover, ivabradine was superior to amlodipine in reducing the rate-pressure product, a parameter of myocardial oxygen consumption, both at rest and at peak exercise.\(^{55}\) The two drugs were also documented as having similar safety.\(^{55}\)

MORE RECENT CLINICAL TRIAL DATA ON IVABRADINE

In the ASSOCIATE (evaluation of the Antianginal efficacy and Safety of the aSsociation Of the \(I_{f}\) Current Inhibitor ivAbradine with a beTa-blockEr) study, Tardif et al.\(^{56}\) evaluated the efficacy of ivabradine in patients with chronic stable angina who were already receiving \(\beta\)-blockers. In this multicenter, double-blind, parallel-group trial, 889 patients with stable angina receiving atenolol 50 mg/day were randomized to receive ivabradine (5 mg bid for 2 months, then increased to 7.5 mg bid for an additional 2 months) or placebo. ETTs were performed on a treadmill using the standard Bruce protocol at pretreatment and at 2 and 4 months following initiation of treatment. The primary end point was change in total exercise duration during ETT from pretreatment to the end of treatment at month 4, assessed at the trough of ivabradine activity. The main findings of this trial were that the total exercise duration (mean±SD) at 4 months increased by 24±65.3 seconds in the ivabradine group versus 7.7±63.8 seconds in the placebo group \((P<0.001)\) and that there were

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**Table 1. Potential mechanisms of benefits of ivabradine in coronary artery disease.** Mostly based on experimental data, from references in text.
significant dose-dependent improvements in all ETT criteria with ivabradine versus placebo (Figure 2). Of particular note, significant improvements in all ETT criteria were detected at both 2 months and 4 months, thus demonstrating the efficacy of both doses of ivabradine.

More recently, the combination of ivabradine and bisoprolol was evaluated in 50 patients with stable angina and chronic obstructive pulmonary disease. Prior to randomization to bisoprolol monotherapy or the combination, all patients received bisoprolol, which was uptitrated as tolerated. The combination of bisoprolol and ivabradine not only adequately lowered HR and optimized antianginal efficacy without raising safety concerns, but also led to improved quality of life, decrease in hospitalization, and reduction in the need for inhaled bronchodilatory therapy compared with bisoprolol monotherapy. In a double-blind, parallel-group study involving 386 patients with chronic stable angina, López-Bescós et al studied the long-term use of ivabradine by randomizing patients to receive ivabradine 5 mg bid or 7.5 mg bid for 2 months. The efficacy end point was a reduction in the number of angina episodes per week and the use of short-acting nitrates from baseline to month 12.

The investigators observed a significant reduction in angina episodes per week at month 12 versus baseline, with HR reductions of 9 bpm and 12 bpm with ivabradine 5 mg bid and 7.5 mg bid, respectively. Apart from being investigated in controlled clinical trials, ivabradine also has also been studied in the context of routine clinical practice. In the multicenter REDUCTION study (Reduction of ischemic Events by reDUCtion of heart rate In the treatment Of stable aNgina with ivabradine), Köster et al enrolled 4954 ivabradine-treated patients with stable angina and followed them for 4 months. They observed significant reductions in HR, the number of angina episodes per week, and the use of short-acting nitrates in these patients.

The BEAUTIFUL study (mortality-morbidity EvAluAtion of the I inhibitor ivabradine in patients with coronary disease and left-ventricular dysfunction) was a randomized, double-blind, multicentered, placebo-controlled trial that evaluated whether HR lowering with ivabradine would reduce CV death and morbidity in patients with CAD and LV systolic dysfunction. The primary end point of this large clinical trial that enrolled >10 000 patients was a composite of CV death, hospital admission for acute MI, and hospital admission for new onset or worsening heart failure (HF). With a median follow-up of 19 months, ivabradine decreased HR by 6 bpm (corrected for placebo), but did not have a significant effect on the primary end point. However, in the prespecified subgroup analysis of patients with HR ≥70 bpm, ivabradine significantly reduced second-
In another analysis of the BEAUTIFUL trial, Fox et al reported that in patients with CAD and LV systolic dysfunction, a HR of ≥70 bpm was associated with significantly increased risks for CV death, hospital admission for HF, hospital admission for MI, and revascularization. Moreover, mortality and HF outcomes (which were more pronounced than outcomes related to CAD) increased continuously with HR beyond 70 bpm. In another post hoc analysis, Fox et al observed that in patients with limiting angina at baseline in the BEAUTIFUL trial, ivabradine was associated with a 24% reduction (hazard ratio, 0.76; 95% CI, 0.58-1.00) in the primary end point and a 42% decrease in hospitalization for fatal and nonfatal MI (hazard ratio, 0.58; 95% CI, 0.37-0.92). Significant reductions in hospitalization for MI and in coronary revascularization were observed in patients with HR ≥70 bpm.

**CLINICAL TRIAL DATA ON IVABRADINE IN SPECIFIC POPULATIONS OF PATIENTS WITH CAD**

In a pooled analysis of 5 studies, Borer and Tardif evaluated the pharmacokinetics and pharmacodynamics of ivabradine in 539 diabetic subjects (18% of all subjects) compared with those in nondiabetic subjects. Compared with nondiabetic patients, diabetic subjects were older and more likely to be female. In addition, a greater proportion of diabetic subjects had Canadian Cardiovascular Society class III angina compared with nondiabetic subjects. Similar pharmacokinetics were observed, regardless of the presence or absence of diabetes. Despite a higher resting HR in diabetic subjects, there was a similar reduction in HR with both ivabradine and atenolol, regardless of diabetes mellitus status. Time to 1-mm ST-segment depression and time to onset of angina on ETT were also similar.

Recently, Skalidis et al studied the effects of ivabradine on coronary flow velocity and coronary flow reserve in 21 patients with stable CAD undergoing diagnostic angiography. These investigators reported that ivabradine (5 mg bid) significantly reduced HR and augmented hyperemic coronary flow velocity and coronary flow reserve, which could potentially improve microvascular function.

In the echocardiographic substudy of the BEAUTIFUL trial in 525 patients from 86 participating centers (426 patients with echocardiograms of adequate quality), a potential benefit of ivabradine in reversing adverse postinfarction remodeling was observed, evidenced by a reduction from baseline in the primary end point, left ventricular end-systolic volume index (LVESVI), and an improvement in left ventricular ejection fraction (LVEF). The effect on LVESVI was related to the degree of HR lowering. In contrast, among placebo-treated patients, LVESVI increased from baseline and LVEF did not change significantly. Furthermore, preliminary data in patients with anterior MI and reduced LV function who were randomized to receive metoprolol or ivabradine 12 hours after successful percutaneous coronary intervention also suggest that ivabradine potentially protects the myocardium, improving LV systolic function and reducing LV end-systolic and end-diastolic volumes.

Tendera et al analyzed pooled data from five randomized clinical trials of ivabradine in patients with stable angina to evaluate the efficacy of ivabradine in different subpopulations, defined according to age, sex, disease characteristics, and comorbidities. Subpopulation characteristics included: severity of angina; history of MI, cerebrovascular disease, revascularization status; and presence of diabetes, asthma, chronic obstructive pulmonary disease, or peripheral vascular disease. The investigators found that the efficacy of ivabradine was similar across all the subpopulations, regardless of the severity of angina or the presence of a comorbidity, and that ivabradine was well-tolerated by all subjects. Most recently, an abstract by Koziolova et al reported positive preliminary findings regarding renoprotection with ivabradine, which confers potential renoprotective effects when included as part of medical therapy for treating patients with stable angina, HF, and renal dysfunction, based on favorable estimated glomerular filtration rate and renal extracellular collagen matrix results.

**SAFETY AND TOLERABILITY**

Ivabradine is a pure HR-lowering drug that has no significant effects on myocardial contractility or other hemodynamic parameters. Moreover, ivabradine does not significantly affect ventricular repolarization or other electrophysiological parameters.

Indeed, the safety and tolerability of ivabradine have been demonstrated in multiple clinical investigations. The most common adverse reactions are luminescent phenomena, known as phosphenes (visual sensations that are induced by stimuli...
other than luminance changes and that may be characterized by increased brightness in the visual field, and bradycardia, both of which are dose-related.

The above visual changes may be explained on the basis that ivabradine can interact with the visual system via inhibition of the $I_h$ current (hyperpolarization-activated current) in retinal cells, which resembles $I_h$. This effect is reversible with complete resolution of symptoms upon discontinuation of ivabradine, with no known toxic effect of ivabradine on the retina. However, any effect of prolonged use of ivabradine beyond 1 year on retinal function remains to be determined.

Notably, in the ASSOCIATE trial, the incidence of visual symptoms were much lower than those reported in previous trials. Visual symptoms (phosphenes and blurred vision) were reported by 9 ivabradine-treated patients (2%) compared with 4 (1%) placebo-treated patients. In the 12-month study by López-Bescós et al. with ivabradine 5 mg bid or 7.5 mg bid, mild transient visual symptoms were the most frequently reported adverse event (23 of 198 patients treated with ivabradine 5 mg bid and 43 of 188 patients treated with ivabradine 7.5 mg bid). These symptoms, which occurred mainly during the first month of treatment, necessitated the withdrawal from the study of only 4 patients.

In ASSOCIATE, the combination of ivabradine and β-blocker (atenolol 50 mg po od) was well tolerated, with only 1.1% of patients withdrawing due to sinus bradycardia in the ivabradine-treated group. In addition, in patients who were taking β-blockers in the BEAUTIFUL trial, concomitant use of ivabradine was observed to be safe (87% of the participants were receiving β-blockers in addition to the study drugs). Furthermore, in the Holter sub-study of the BEAUTIFUL trial (840 subjects who received ivabradine 5 mg or 7.5 mg bid or placebo), there was no increase in conduction disturbances or rhythm abnormalities in ivabradine-treated subjects versus placebo-treated controls. The main HR findings during Holter monitoring are presented in Figure 3.
Indeed, from available clinical trial experience to date, the incidence of bradycardia (HR <40 bpm) with ivabradine is very low, which may be explained, at least in part, by the property of use-dependence. Moreover, in the analysis by Borer and Tardif, frequencies of sinus bradycardia and visual disturbance were similar across subjects, regardless of the status of diabetes.

As a pure HR-lowering drug, ivabradine may potentially be used alone, as an alternative to β-blockers in patients who are unable to tolerate β-blockers, or in combination with β-blockers. In addition, the use of ivabradine in combination with a β-blocker may facilitate the lowering of the dosage of β-blockers, while maintaining adequate HR control. It is worth noting that bronchoconstriction, a known adverse effect of β-blockers, does not appear to be associated with ivabradine even in asthmatic subjects. Consistent with the safety observations in the ASSOCIATE trial (evaluating the combination of atenolol and ivabradine), a more recent study that evaluated the combination of bisoprolol (at patient-tolerated doses) and ivabradine reported good tolerability of this drug combination in patients with stable angina and chronic obstructive pulmonary disease.

In addition, Babu et al recently conducted a double-blind, placebo-controlled crossover study in 20 subjects with asthma to evaluate the effects of repeated administration of ivabradine on pulmonary function in asthmatic subjects who had been stabilized for at least 4 weeks on inhaled corticosteroid therapy. These subjects were randomized to receive placebo or ivabradine 10 mg po twice a day for 4.5 days, which was followed by a washout period of 2 days, and then crossed over to receive either ivabradine or placebo. There was no significant effect observed on the main outcome variables for respiratory function, which consisted of forced expiratory volume in 1 second (FEV1) and peak expiratory flow rate (PEFR), and no difference in the symptoms of asthma or in the use of inhaled salbutamol.

Selective β1 inhibition may circumvent other untoward effects of β-blockade in specific clinical circumstances, such as a prohibitive fall in blood pressure in the setting of hypotension at baseline, negative inotropic effects, fatigue, and sexual dysfunction. Moreover, as β-blockade delays isovolumic ventricular relaxation and augments α-vasoconstriction secondary to displacement of norepinephrine and epinephrine from β- to α-adrenergic receptors, coronary blood flow may be compromised (whereas the above would not be expected with ivabradine). Furthermore, β-blockers may have undesirable metabolic effects. For instance, in patients with CAD, chronic β-blocker use is associated with an elevated risk of developing new-onset diabetes. In contrast, ivabradine has no adverse effects on glucose metabolism.

In patients with stable CAD, no rebound angina was observed upon cessation of ivabradine. With regard to combination therapy for angina, there are no known safety issues with the concomitant use of ivabradine and nitrates. Dihydropyridine CCBs (amlodipine, lacidipine) do not have a significant effect on the pharmacokinetics and pharmacodynamics of ivabradine. However, concurrent use of verapamil or diltiazem, which are moderate inhibitors of CYP3A4, increases ivabradine exposure, with a 2- to 3-fold increase in the area-under-the-curve (AUC), which was associated with a HR lowering of 5 bpm.

The combined use of ivabradine and verapamil or diltiazem cannot therefore be recommended.

In terms of potential interactions with other drugs, coadministration of ketoconazole, a potent CYP3A4 inhibitor, with ivabradine increases the maximal plasma concentration of ivabradine. Induction of ivabradine metabolism by Hypericum perforatum (St John’s Wort), a CYP3A4 inducer, has been reported in healthy subjects. An interaction between ivabradine and carbamazepine, another CYP3A4 inducer, in healthy subjects has been documented, with the bioavailability of ivabradine being lowered by about 80% with concurrent use of carbamazepine.

**FUTURE DIRECTIONS**

Future prospective clinical trials are warranted to further evaluate the HR-lowering benefits of ivabradine in different patient subpopulations with chronic CAD and to explore whether ivabradine may have a therapeutic role in acute presentations of CAD. Furthermore, proof-of-concept studies are needed to evaluate the therapeutic potential of the novel mechanisms of action of ivabradine in patients, both for the treatment of HR and of diseases in other vascular territories.

**CONCLUSION**

Ivabradine is an important recent advance in the treatment of chronic stable angina. Future studies are needed to explore its full therapeutic potential in CV medicine.

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ivabradine and carbamazepine in healthy 
volunteers. 
This essay was prompted by an encounter with a group of medical students in a recent discussion on the renin-angiotensin system and essential hypertension. Perhaps predictably, the students were somewhat disbelieving when told that sixty or more years ago, there was no proven therapeutic treatment for essential hypertension. For example, Paul Wood, in the chapter on hypertensive heart disease in his classic textbook, Diseases of the Heart and Circulation, states that “it must be said at once that as yet there is no satisfactory treatment for essential or malignant hypertension.”

As illustrated in the earlier essays on cardiovascular drug discovery, progress was greatly facilitated by the invention of new technologies, an aid to improving diagnostic accuracy and the effects of novel therapies. Thus, the invention of the platelet aggregometer triggered large advances in that field of therapy, as did Eindhoven’s invention of the electrocardiograph, which was exploited by Thomas Lewis in classifying cardiac arrhythmias. In the context of hypertension, the invention and development of the sphygmomanometer between 1883 and 1901 transformed the understanding of this condition. The key advances were first-ly the invention of the mercury sphygmomanometer by Riva-Rocci in 1896, and the use of auscultatory measurement of systolic and diastolic pressure by Korotkoff in 1906, working in the Institute of Military Medicine in St Petersburg, Russia.

Prior to these advances, clinicians debated whether the suspected, but unmeasured, condition should be termed hypertension, hypertonia (as favored in Europe), or hyperpiesia (a term coined by the eminent London physician Clifford Allbutt).

Of the numerous advances made in understanding the nature and clinical importance of hypertension between 1915 and 1930, two publications were pivotal. Firstly, Hunter analyzed the relationship between age and blood pressure in healthy US subjects. He observed that from an average blood pressure of 120/88 mm Hg at age 20 years, it rose to 135/89 mm Hg at age 60 years. In collaboration with Rogers, he later showed that a blood pressure of 120/88 mm Hg at age 20 years, it rose to 135/89 mm Hg at age 60 years. He observed that from an average blood pressure of 120/88 mm Hg at age 20 years, it rose to 135/89 mm Hg at age 60 years. In collaboration with Rogers, he later showed that a blood pressure of 120/88 mm Hg at age 20 years.

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PATHOPHYSIOLOGY OF HYPERTENSION

It will become apparent in relating the evolution of understanding of the pathophysiology of hypertension as well as its management that the field is characterized by investigators with strongly held, polarized views on both these topics. For example, the identification of Bright disease led to the view that all hypertension was secondary to some form of renal disease. Over time, however, several investigators observed that marked hypertension could be associated with normal renal function. A major contribution to this debate was made by Wagner and Keith in 1924, who observed that patients with severe hypertension, accompanied by marked retinopathy, also had adequate renal function. They termed this syndrome malignant hypertension. Of their 81 cases, 90% died within 51 months of diagnosis. Four years previously, the eminent German pathologist Aschoff claimed that “hypertony” did not lead to atherosclerosis, but to hypertrophy of the entire vascular system. There are numerous other examples of conflicting views concerning both the cause and progression of hypertension.

For example, Alfred Mantle in a paper, entitled “The treatment of confirmed cases of high blood pressure, the undesirability of actively applying therapeutic means to reduce it,” based on a symposium held at the Royal Society of Medicine, London, in 1913, stated that “lastly, we must not use any active means to reduce the pres-
Early 20th-century theories on the etiology of hypertension

| Primary renal origin (Volhard and Fahr) | Arteriolar hypertrophy (Keith, 1924) | Central vasomotor hyperactivity leading to functional arteriolar change (Kahler, 1924) | Chemical factors, such as excess urea, uric acid, sodium chloride, calcium, guanidine, adrenaline, or cholesterol |

Table I. Theories on the etiology of hypertension from 1920-1930.

sure, remembering that it is probably an advantage and necessary that the pressure should be high for the maintenance of an adequate supply of blood to vital organs. The wide range of hypotheses as to the possible causes of hypertension is summarized in Table I. The prevailing view in the period between 1915 and 1930 was that the cause of hypertension was identified, then treatment would become obvious.

INITIAL THERAPEUTIC APPROACHES

The range of theories on the etiology of hypertension, as summarized in Table I, resulted in an equally diverse approach to the management of hypertension. By the 1930s, the therapeutic strategy comprised: identifying the sources of vasomotor instability and stimulation, and determining the mechanisms underlying these stimulations.

Given that there was a reasonable consensus among clinicians at that time as to the possible role of central and peripheral nervous activity in causing raised heart rate and blood pressure, treatment focused initially on modifying the patient’s lifestyle to reduce bodyweight and mental tension. These elements remain the fundamental principles of management of hypertension today. There was impressive evidence placed on dietary manipulation comprising a range of increasingly prescriptive menus, the most extreme examples, including F. M. Allen’s salt-free diet, which he claimed was more successful than other measures used at that time.14 This opinion was not corroborated by other investigators. A subsequent example of dietary manipulation was Kempener’s “rice diet,” introduced in the 1940s.15 Undoubtedly, reduction of salt intake below 200 mg daily is a desirable adjunct, either for the prophylaxis or the management of hypertension, as well as an adjunct to effective therapy. The drugs used to treat hypertension in the 1930s are listed in Table II.16 The different medications reflect either an attempt to dilate blood vessels or induce sedation in the patient. At this time, investigators did perform limited dose-response studies with, for example, bromide and icodide, but all the studies were both brief and uncontrolled. The confused state of drug treatment is exemplified by studies using parenteral administration of liver extract, in which 40%-60% of patients claimed blood pressure was reduced, but 90% of whom obtained symptomatic relief without reduction in their blood pressure.17

An apparently more effective treatment was potassium sulfoxycyanate given at doses of about 0.2 g two or three times daily.18 This treatment caused a reduction in blood pressure of between 20 and 60 mm Hg. A related analogue, thiocyanate, became increasingly popular over the next twenty years. Its mode of action was disputed, but it was later shown to increase renal excretion of sodium, possibly by inhibiting carbonic anhydrase, thus anticipating the later discovery of diuretics.19,20

However, the use of thiocyanates was associated with rashes, joint pains, and hypothyroidism, as well as electrolyte loss.

NONDRUG APPROACHES

D’Arsonvalization

This was a form of electrical diathermy first introduced in France by Dr J. A. d’Arsonval. This technique comprised either local or general application of high frequency impulse current (110-400 kHz) at low strength (100-200 mA). It was claimed to have a range of effects on biological systems. The eminent Clifford Allbutt, inventor of the clinical thermometer, stated in the mid-1920s that “d’arsonvalization by the autocondensation method is the most valuable immediate aid we possess for hyperpiesia.” This view was endorsed by others.21 However, this technique soon fell into disuse.

In the 1920s, there were many alternative approaches claimed to reduce blood pressure (summarized in Table III). For example, Dr Fortescue Fox published a detailed review on the different types of baths and spa waters.22 The rationale was to reduce arteriolar spasm and to diminish “all nervous excitation.” The wide range of recommended interventions perhaps reflects the lack of understanding at that time, of the mechanisms involved in essential hypertension, though clearly the physicians recognized the role of the central and peripheral nervous system. Presumably it was this recognition that led to the introduction of surgical sympathectomy to achieve the same purpose.

Surgical interventions

Removal of the midthoracic to the upper lumbar sympathetic chains became popular in the 1930s. The rationale was to reduce autonomic-mediated vasoconstriction in hyper-
While there was an immediate reduction in blood pressure postoperatively, only 21% of patients had any significant reduction in blood pressure five years later. It is however noteworthy that in individual patients with malignant hypertension, surgical sympathtectomy rapidly reversed the associated cardiac hypertrophy and retinopathy. Given the unpredictable response and perioperative mortality, this approach was abandoned. It did, however, emphasize the potential role of inappropriate autonomic activity in essential hypertension, which provided an impetus to achieve similar effects by chemical rather than surgical means.

**FIRST-GENERATION ANTIHYPERTENSIVE AGENTS**

During the 1940s, there was a paradigm shift in the approach to reducing blood pressure. A range of drugs was discovered with different modes of action, namely reduction of central nervous system activity (veratrum alkaloids, ergot, reserpine) and modulation of either autonomic tone (ganglion blockers, guanethedine) or direct vasodilatation (hydralazine, prazosin).

These advances were made by a combination of factors including improvements in basic pharmacological techniques and the emergence of brilliant clinical scientists, such as Freis and Page in the USA, Smirk in New Zealand, Pickering in the UK, and Gross and Volhard in Germany. The contribution made by these and other investigators in relation to novel drugs is briefly summarized below.

**Ganglion blockers**

In 1948, Paton and Zamis published a paper in *Nature* describing the potential clinical application of bisquaternary salts possessing neuromuscular

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**First-generation antihypertensive medications - Fitzgerald**

<table>
<thead>
<tr>
<th>Substance</th>
<th>Dosage</th>
<th>Method of administration</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amyl nitrite</td>
<td>3 min (&quot;pearls&quot;)</td>
<td>Inhalation</td>
<td>Immediate, transient vasodilatation</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>1/200 to 1/100 grains</td>
<td>Tablet</td>
<td></td>
</tr>
<tr>
<td>Sodium nitrite</td>
<td>1/2 to 2 grains two to four times a day</td>
<td>Tablet</td>
<td>Rapid, more prolonged vasodilatation</td>
</tr>
<tr>
<td>Erythrol tetranitrate</td>
<td>1/2 to 1 grain two to three times a day</td>
<td>Tablet</td>
<td></td>
</tr>
<tr>
<td>Bismuth subnitrate</td>
<td>5 to 9 grains three to four times a day</td>
<td>Tablet</td>
<td>Gradual, prolonged vasodilatation</td>
</tr>
<tr>
<td>Sodium bromide</td>
<td>5 to 15 grains one to three times a day</td>
<td>Tablet</td>
<td>Sedative, vasodilatation</td>
</tr>
<tr>
<td>Chloral hydrate</td>
<td>5 to 15 grains one to three times a day</td>
<td>Elixir</td>
<td>Sedative</td>
</tr>
<tr>
<td>Potassium bromide</td>
<td>aa 1/120 grains (5 mg) three times a day (with or without chloral hydrate 0.25 g)</td>
<td>Elixir</td>
<td>Slow, greatly prolonged vasodilatation</td>
</tr>
<tr>
<td>Potassium iodide</td>
<td>1/2 grains one to three times a day</td>
<td>Tablet</td>
<td></td>
</tr>
<tr>
<td>Potassium sulphocyanate</td>
<td>0.1 g ampoule one to two times a day</td>
<td>Subcutaneous injection</td>
<td>Rapid, fairly prolonged vasodilatation</td>
</tr>
<tr>
<td>Liver extract</td>
<td>0.5 to 5 mL one to three times a week</td>
<td>Intramuscular injection</td>
<td></td>
</tr>
<tr>
<td>Cucurboxtin</td>
<td>50 to 150 mg one to three times a day</td>
<td>Capsules</td>
<td></td>
</tr>
</tbody>
</table>

**Ganglion blockers**

In 1948, Paton and Zamis published a paper in *Nature* describing the potential clinical application of bisquaternary salts possessing neuromuscular

**Table II. Examples of drugs used to treat hypertension in the 1920s.**


**Table III. Nondrug remedies used to treat hypertension, 1920-1940.**

and ganglion-blocking activities. The lead compounds were hexamethonium bromide (C6) and pentamethonium, the former being given intravenously, intramuscularly, subcutaneously, or orally. Administration to hypertensive patients caused an immediate reduction in blood pressure, particularly in an upright position, following an oral dose of 125 mg three times a day.

Between 1949 and 1953, numerous publications showed that various ganglion-blocking agents reduced blood pressure in patients with severe hypertension. A notable study from Smirk’s group in New Zealand in 1951 reported on the effects of these agents in 150 patients, including 11 with malignant hypertension. It was concluded that “almost all hypertensives can have their blood pressure controlled by these drugs.”

Tolerance to ganglion-blocking drugs develops in most patients. Side effects were common, including visual disturbances, ileus, postural hypotension, and urinary dysfunction. The only analogue that is still available is mecamylamine, and newer antihypertensive agents have supplanted the use of ganglion blockers in hypertension. However, as one of the first-in-class oral antihypertensive agents, it did demonstrate that drug therapy could cause a sustained reduction in elevated blood pressure.

**Veratrum alkaloids**

The alkaloids of *Veratrum viride* were characterised by Craig and Jacobs in 1943. They are chemically related to steroid hormones and glycosides. They are natural products isolated from the potato as solanidine. Originally, the natural product was used to control blood pressure in eclampsia.

Oral preparations include vertavis (mixed alkaloids from *V. viride*), vertiloid (a purified form of vertavis), and anatensol, the most highly purified mixture from *V. viride*. The most potent *Veratrum* alkaloids are protoveratrine a and b, isolated from *V. album*.

The acute and chronic use of all preparations of these products have been studied in essential hypertension, with widely varying results. A major limitation was the narrow margin between obtaining blood pressure reduction and causing emesis. The hemodynamic effects comprised a reduction in heart rate and peripheral vasodilatation. These effects were attributed to activation of the cardiac afferent vagal nerve fibers, and possibly also an effect on the central nervous system. No direct relaxing effect on arterial smooth muscle was observed. The positive aspect of these products, as described by Freis, was that blood pressure was reduced without impairing either cardiac or renal function. The high incidence of emesis was a major clinical disadvantage and was closely related to the neurally-mediated hemodynamic effects. So, the possibility of eliminating the emetic effects with purified compounds is unlikely.

**Ergot alkaloids**

Chemical purification of the components of a crude extract of ergot (Figure 1) identified five alkaloids in 1943, following hydrogenation of the lysergic acid component, Stoll and Hoffman identified dihydroergotamine, dihydroergocristine, and dihydroergocornine (DHO180), as well as dihydroergocryptine (DHK135), while working for the Sandoz Company, Switzerland. Subsequent pharmacological studies by Rothlin, also working at Sandoz, showed that DHO180 had only sympatholytic actions without the normal direct vasoconstriction action of ergot and ergotamine tartrate (Gynergen). In a detailed hemody-
namic study in hypertensive subjects, Freis and colleagues confirmed that DHO180 had sympatholytic effects in patients, possibly mediated by a central action rather than peripheral sympathetic blockade. They suggested that because of widely varying net hemodynamic effects, sympatholytic agents, including DHO180, had fundamental limitations as a form of therapy in hypertension.

**Rauwolfia analogues**

Reserpine is obtained from the root of the *Rauwolfia serpentina* plant, which is a member of the Apocynaceae family (Figure 2). The root of the plant was widely used in Asian countries to treat fevers, insomnia, and even mania in the 1930s, extensive chemical and pharmacological studies identified a range of alkaloids that reduced both heart rate and blood pressure experimentally. It also relaxed vascular smooth muscle. The dried root was marketed in India in the 1930s with sales in excess of 50 million tablets. In 1949, Vakil, who was working in the Cardiovascular Department of the Memorial Hospital in Bombay, published a pivotal observational study on the effects of one Serpina tablet, a commercially available *Rauwolfia* preparation, given three times a day to 50 hypertensive patients for four weeks. In 62% of these patients, there was either a moderate (20/10 mm Hg) or marked (25/15 mm Hg) reduction in both systolic and diastolic pressures. There was no evidence of tolerance on prolonged treatment and no serious ill effects were observed. Subsequently, three pure alkaloids were identified. The alkaloid reserpine was synthesized in the Ciba AG laboratories, Basel, in 1949. It was shown to cause marked reduction in blood pressure in dogs at an oral dose of 0.1 mg/kg. After, it was shown to be a clinically effective hypotensive agent at doses between 0.5 mg and 1.0 mg daily. It caused bradycardia accompanied by a tranquilizing action. These properties were subsequently shown to be due to depletion of noradrenaline, dopamine, and serotonin in selected brain areas. It also inhibited noradrenaline reuptake and deposition in peripheral sympathetic nerves. Clinical studies reported a wide range of dose-dependent side effects, including fatigue, fluid retention, and central nervous system disturbances, including depression and agitation. Despite these problems, reserpine became the drug of choice in the 1950s for treating moderate hypertension.

**Peripheral vasodilators**

The practice of surgical resection of sympathetic nerves in the management of severe hypertension in the 20 years before 1950 focused attention on finding drugs that would relax vascular smooth muscle without producing the marked side effects of ganglion-blocking drugs. Page pioneered the potent vasodilator sodium nitroprusside, which caused a dramatic reduction in blood pressure in severe hypertension. Unfortunately, it had to be given intravenously so its application was confined to the hypertensive crisis of malignant hypertension. The first orally effective vasodilator was hydralazine (apresoline), discovered in the Ciba AG laboratories in 1950. Hydralazine caused a prolonged reduction in blood pressure, accompanied by a reflex-mediated tachycardia. It is concentrated in the walls of arterial and venous blood vessels, but its precise mode of action is still unknown. It reduces blood pressure without affecting renal perfusion, which was an attractive pharmacological profile. However, it also caused a dose-dependent headache and tachy-
cardia, and it also had a short half-life, requiring dosing of 25 mg three to four times daily up to a maximum of 400 mg daily. Its main limitation was the occasional occurrence of a lupus erythematosus–like syndrome, as well as tolerance to its hypotensive effects. However, at low doses, in combination with both reserpine and a thiazide diuretic, it was subsequently shown to be very useful.44

**Adrenergic receptor blockers**

By the late 1940s, it was known that the peripheral sympathetic nervous system mediated contraction of vascular smooth muscle by catecholamine-mediated activation of \( \alpha \)-adrenoceptors. It was Raymond Allquist who, in 1948, coined the term \( \alpha \)-receptor, based on the rank order of potency of the catechoamines adrenaline, noradrenaline, phenylephrine, and isoprenaline.45 Specific blockade of vascular \( \alpha \)-receptors reduces hypertension due to catecholamine-secreting pheochromocytomas, but the effects in essential hypertension are unpredictable. The drugs developed were phenoxybenzamine (dibenzyline), a noncompetitive \( \alpha \)-adrenoceptor antagonist, and piperoxan (benzodioxine) and phen tolamine (regitine), competitive antagonists. This class of drugs is associated with postural hypotension and reflex-mediated tachycardia, as well as tolerance with prolonged use. They were therefore unsuitable as monotherapy for treating essential hypertension.46

**COMMENTARY**

The challenge posed by essential hypertension in the first half of the twentieth century was due to the intense polarization of opinions as to its etiology, with the consequence that approaches to therapy were equally diverse, as reflected in Tables II and III. Progress in the field was made possible by the commitment of a number of outstanding clinical scientists. Those knowledgeable in this field will have their own icons. The author’s icons are listed in Table IV, and reflect possibly an Anglo-Saxon bias, since space does not permit discussion of the numerous contributors to the field of hypertension research.

The question that led to prolonged medical debate between 1920 and 1966 was: “does sustained reduction in raised blood pressure reduce the incidence of cardiovascular morbidity and mortality?” Patients with malignant hypertension who underwent surgical sympathectomy certainly survived longer than those not treated, but they represented only a fraction of the hypertension population. It was Professor Edward Freis (1912-2005) who finally showed conclusively, by organizing the Veterans Administration Cooperative Study, that controlling elevated blood pressure by administration of reserpine, hydralazine, and chlorothiazide dramatically reduced the incidence of strokes, congestive heart failure, and renal dysfunction.47 Two of the three drugs used in that trial were discovered between 1940 and 1954, while chlorothiazide was the first of a new generation of effective antihypertensives developed by Merck and Company.48 Freis started his career in Boston in 1946 under Professor Wilkins. The first drug that they studied for its effects on raised blood pressure was the antimalarial compound pentaquine, which caused postural hypotension in volunteer subjects. A patient with severe hypertension, who was rejected as too high a risk for sympathectomy, had a diastolic blood pressure of 160 mm Hg reduced to 100 mm Hg by the administration of pentaquine.49 It was shown much later that quinidine analogues, such as pentaquine, block \( \alpha_1 \) and \( \alpha_2 \) adrenoceptors, which reduces blood pressure by inhibiting peripheral sympathetic tone.50 This observation prompted Freis to seek novel antihypertensive therapies for the next 40 years, culminating in the award of the Lasker Prize for Medicine in 1971.

A second icon is Professor Irvine Page (1901-1991), who identified a compound, called angiotension, at the same time as Braun Menindez, who called it hypotension—this compound is better known today as angiotensin. Page also was associated with the discovery of serotonin51 and the role of renal nerves in renal hypertension. His most notable contribution was probably the development of his mosaic theory of hypertension.52 This refuted the widely held opinion of many clinicians that there was a “cause” of hypertension. In a masterly review given at a Ciba-sponsored symposium in 1966, he concluded, “the past three decades have indeed been a golden age in the understanding and treatment of hypertension...the work will, I believe, stand as a model of clear thinking, prudent financing, and lack of exaggerated claims...if during the next thirty years as much is accomplished, the disastrous effects of hypertension on civilised man may well be at an end.”53 Page also had a deep knowledge of chemistry and had been a member of the American Chemical Society from the age of fourteen. He was invited to establish a department of brain chemistry at the Kaiser Wilhelm Institute in Munich in 1928. This combination of basic science and clinical understanding is probably key to what made his contribution so notable.
My third icon is Sir Horace Smirk, who was born in the UK in 1902, but worked abroad first in Egypt and subsequently in New Zealand for most of his professional life. He was trained at University College, London, and set up a research-based clinical department in the University of Dunedin in New Zealand. Smirk was amongst the first investigators to evaluate ganglion blockers in essential hypertension, giving hexamethonium or pentamethonium by subcutaneous injection at low doses, the dose being individualized for each patient. His hypertension clinic was characterized by meticulous attention to detail and close involvement of the nursing staff. He played a major role in developing the concepts of combination therapy in the management of essential hypertension.

Table V (A and B). Currently available classes of antihypertensive drugs and dates of their introduction to the market.

<table>
<thead>
<tr>
<th>First agent (date of introduction)</th>
<th>DIURETICS</th>
<th>Currently approved agents</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Thiazides</td>
<td>Bendroflumethiazide</td>
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Table V (A and B). Currently available classes of antihypertensive drugs and dates of their introduction to the market.
My two remaining icons are Sir George Pickering (1904-1980) and Professor Franz Gross (1913-1984). The former became Regius Professor of Medicine at Oxford University and published a classic book on high blood pressure in 1955. In a provocative after-dinner speech in 1978, reflecting on the treatment of mild hypertension, he commented: “I have liberated my patients from depression with rauwolfia and lassitude with α-methyldopa. Fortunately, treatment isn’t like that anymore.”

Professor Franz Gross worked at Ciba AG, Basel, for 21 years, in both the Biological Research Department and subsequently as Director of the Medical Department. He specialized in antihypertensive drug research, including ganglion blockers (Ciba 9295), the vasodilator hydralazine, and reserpine. He made notable contributions on the role of the kidney in hypertension. In 1968, he became Professor of Pharmacology at the University of Heidelberg, subsequently holding senior executive roles in several learned societies. The author worked in his department in Ciba, but sadly failed to appreciate Franz’s scientific stature.

**PHARMACEUTICAL INDUSTRY CONTRIBUTIONS**

The majority of the first-generation antihypertensive drugs were either discovered or developed by at least a dozen pharmaceutical companies in the USA and Europe between 1945 and 1953. In reviewing the relevant literature of that period, one is struck by two features. Firstly, none of the publications on clinical trials of the emerging novel antihypertensive compounds makes any reference to ethics committee approval for the research. Clearly, it was a markedly different operating environment compared with the 21st century. Secondly, in the UK, the time between synthesis of the drug and clinical use was 1-2 years. In 1953, Dr Alfred Spinks, Research Director of the ICI Pharmaceuticals Division, prepared a strategic research review including the amount of resources invested in research on cardiovascular topics in the USA. He concluded that 61% of resources were devoted to hypertension research, and these resources were divided as follows: veratrum 20.5%, antiadrenaline compounds 19.5%, ganglionic blockade 13.5%, and vasodilators 7.5%. Spinks recommended a major investment in hypertensive research.

In contrast to the clearly defined requirements of the US drug regulatory system, the British drug safety regulation system was fragmented, and usually put in place retrospectively. This might explain the apparent ease with which novel compounds underwent rapid clinical evaluation. Fortunately, evaluation of novel drug candidates in the 21st century requires well-defined and enforced criteria. In spite of this, modern clinicians have a range of effective antihypertensive drugs, which are often prescribed in combination (Table V, page 215).

This table, which lists antihypertensive agents with widely differing modes of action, is a testament to the contribution the research-based pharmaceutical industry has made to the treatment of a chronic disease. The range of therapeutic options provides clinicians with such an armamentarium that in the majority of hypertensive subjects, normotensive blood pressure levels can be achieved.

The current challenge is to detect hypertension early and, equally important, to maintain adherence to therapy. It is perhaps ironic that despite the availability of effective therapy, many subjects with essential hypertension are currently either not diagnosed or their blood pressure is inadequately controlled, with potentially serious long-term consequences.

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Angina: Old Concepts Revisited
Summaries of Ten Seminal Papers

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Selection of seminal papers by Jeffrey S. Borer, MD, FACC
Downstate Medical Center and College of Medicine
Brooklyn and New York - NY, USA

Highlights of the years by Ian Mudway, MD
Lung Biology - Division of Life Sciences - Franklin Williams Building
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The medicine, angioplasty, or surgery study (MASS-II): a randomized, controlled clinical trial of three therapeutic strategies for multivessel coronary artery disease: one-year results


*J Am Coll Cardiol.* 2004;43(10):1743-1751

It was in 1989 that I first got my hands on an angioplasty balloon. I couldn’t wait to get into the coronaries and stick it to those stenoses. If I couldn’t be Christiaan Barnard, at least I could be Clint Eastwood and Bruce Willis, saving grateful patients from imminent death from their coronary narrowings. Yet a few miles away from the Hammersmith Hospital where I was training in Cardiology, Michael Davies at St George’s Hospital in London was showing that plaque rupture occurred frequently at sites remote from stenosis. Yet the belief that relief of angina would prevent myocardial infarction was widespread, certainly among patients and the general public and also among most cardiologists.

The MASS-II (Medicine Angioplasty or Surgery Study–II) paper is one of the earliest studies to show that cardiologists racing in with balloons and stents were not the gallant heroes they considered themselves to be. Hueb et al’s paper shows for the first time in a substantial study that medical therapy had fewer adverse events than angioplasty. In this trial of 611 patients, the individuals treated with medical therapy did rather better than those undergoing angioplasty. This was almost heresy at the time, when interventionalists ruled the roost and angioplasty could do no wrong. This seminal paper was the *hors d’oeuvres* to the much larger and even more definitive COURAGE trial (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) published a few years later. Coronary artery bypass grafting had and still has a prominent role for 3-vessel disease or left main stem stenosis, and this is not questioned.

We now know that plaque stabilization is the fundamental goal in cardiology. This is achieved by blood pressure lowering, aggressive cholesterol lowering, and antiplatelet therapy, with angiotensin-converting enzyme inhibitors added if there is overt coronary disease or hypertension. Simply stenting part of the coronary artery does indeed protect a couple of centimeters of endothelium. It does nothing, however, to protect the rest of the coronary tree. While this is obvious now, we were less aware of this a few years ago. Hueb et al, although they did not quite state that conclusion in those terms, provide the data that support the importance of coronary stabilization, rather than stenosis reduction, as the mainstay for cardiovascular protection.

Particularly praiseworthy is that the study was carried out in Brazil rather than in a major American or European center. Hueb et al’s paper paved the way for Brazil as a major force in cardiovascular research and practice. It was really the first study to show the value of medical therapy, when compared with intervention, and this vital study will continue to be cited by current and future cardiovascular physicians, and by historians of cardiac practice in the future.

The United Nations declares 2004 the International Year of Rice—rice is the staple food for more than half the world’s population; buildup of gas inside a dead decomposing sperm whale causes it to explode in a crowded Taiwan urban area, while being transported for a postmortem examination; and Vladimir Putin easily wins second term in Russian presidential election.
When confronted with an individual patient, our daily work tends to be dominated by symptoms, investigation, and treatment of defined conditions, and we rarely have time to sit and think about mechanisms of disease progression, other than hardening of the arteries is caused by high cholesterol, smoking, high blood pressure, and diabetes. Hanson’s article is a timely review of the cellular and biological processes that result in the development of atheroma, and tilts toward an understanding of the Holy Grail of cardiology—plaque rupture. Hanson begins rather disingenuously, suggesting that in 1995 we believed that treatment of high cholesterol and high blood pressure would eliminate coronary disease. This is a mischievous introduction, rather than the truth since by the 1990s we were of course well aware of the risks of family history, poor nutrition, social deprivation, and smoking, just for starters. Even without treatment of cholesterol and blood pressure, the annual incidence of premature coronary disease had fallen steadily since the mid 1980s. This certainly pre-dates statin introduction. Yet, our intrigue is then drawn to review the rest of this very well researched article.

The development of atheroma is really a response to injury. Hanson points out that this injury is fundamentally based on the inflammatory action of too much cholesterol in too many lipoproteins adhering to endothelial cells. Hanson examines in considerable detail the immune mechanisms involved in endothelial cell damage, macrophage accumulation, and lipoprotein depositions. He examines the cellular processes involved, but does not look at the epidemiology of the association of low cholesterol and lack of atheroma. The myriad immunological processes involved in atheroma development are processes that occur at sites of inflammation throughout the body and are applicable to every condition where there is an inflammatory process. Hanson does introduce the idea of immune modification as a treatment for coronary disease, yet such a therapeutic approach would be hard to target to the arterial system without endangering tumor surveillance, and anti-infective and wound healing mechanisms, which are all vital to human existence.

When junior research fellows ask me what they should do research in, I usually say, “plaque rupture.” If we could prevent plaque rupture we could effectively sort out much of cardiology. No one ever died from angina. It is valuable therefore, than Hanson examines in some detail the processes involved in plaque rupture and in plaque erosion, the two mechanisms of sudden plaque progression or coronary thrombosis. Hanson introduces matrix metalloproteinases, a family of enzymes that may be involved in degradation of the plaque surface.

Therapeutic processes to stabilize plaques could conceivably be the real future of the biology that remains a dream rather than an area nearing therapeutic implementation. The role of aspirin is introduced, but this most perennially topical area of subjects is not developed. Even in 2011, we remain uncertain whether aspirin really offers benefit or harm in disease prevention among healthy individuals. Hanson does describe the anti-inflammatory effects of statins. While there is no doubt that these exist, the benefits of statin therapy do seem to be tightly related to the degree of cholesterol lowering, and to my mind, it is the reduced delivery of lipoproteins to endothelial cells, rather than particular benefits on immune cell function, that explains the majority of the benefits of statins.

Finally, Hanson’s article really offers us a glimpse into the complex and interrelated processes involved in atheromatous plaque biology. We have skimmed the surface of our understanding of plaque rupture, which remains the greatest target for therapeutics in cardiology.

The Kyoto Protocol goes into legal effect, after being ratified by 55 countries—but not the United States; Frenchman Alexis Lemaire computes the first 13th root calculation of a 200-digit number; and an explosion at one of BP’s largest oil refineries in Texas City kills 15 and injures more than 170
Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data

A. D. Lopez, C. D. Mathers, M. Ezzati, D. T. Jamison, C. J. Murray

Lancet. 2006;367(9524):1747-1757

This monumental study by Alan Lopez and colleagues is a follow-up to the 1994 study that examined the state of world health in 1990. It gives us a sobering, yet in some ways encouraging picture of the global canvas of disease.

Child health and the cardiologist. In affluent countries child death concerns around 2/1000 children, vs 20 times more in sub-Saharan Africa. The vast majority of these deaths are avoidable, being caused by what ought to be readily treatable infections, poor hygiene, and lack of vaccinations. Noncommunicable disease account for the majority of child deaths among rich countries, yet are a tiny proportion in poor countries. This is a clear call to devote far more research funding toward infectious diseases.

Global burden of cardiovascular disease (CVD). Ischemic heart disease as a cause of premature death has increased almost 50% in 10 years. Ironically, this is largely due to a great increase in CVD among low- and middle-income countries, which in a way is progress, as fewer people are dying from infectious disease, leaving more to die prematurely of CVD and stroke. In my opinion, nonfatal stroke is, above all else, the CVD most feared, most costly to health services, and most destructive to individuals and their families. This leads to an examination of the surprising risk factors identified globally.

Hypertension and global disease. In affluent countries we are quite good at identifying and treating risk factors. It is all the more surprising that hypertension remains the single biggest risk factor for global disease, both in terms of premature death and in disability, substantially outweighing smoking, cholesterol, and obesity. I recently examined a doctoral thesis from a cardiologist in Nigeria, examining blood pressure in a stable farming population in the northern part of the country. The awareness that blood pressure existed, yet alone could be high and cause stroke, was almost nonexistent. Measuring blood pressure is cheap and incredibly effective in identifying disease. Treatment is also cheap. A thiazide and a calcium channel blocker in affluent countries cost a few pence or cents per month, and would successfully treat low-renin hypertension, so prevalent in sub-Saharan Africa, costing next to nothing in global terms. There are now plenty of angiotensin-converting inhibitors off patent, and triple therapy could be used as required. Subsequent monitoring would be largely unnecessary. While the polypill is a great idea and has certainly been trialed now, a simple thiazide-calcium blocker combination would go a very long way to reduce stroke, heart failure, and to a lesser extent coronary disease.

Concluding thoughts. Affluent countries will continue to strive for faster delivery of acute myocardial infarction care, optimum treatment for heart failure, transplantation, cardiac surgery, and the latest developments in cardiovascular medicine. Yet across the world, CVD prevention, or at least delay, must be the mainstay of health care strategy. The inexorable rise of diabetes is largely due to changes in lifestyle and diet. This is easy to write, but harder to treat. High cholesterol is also readily treatable if it can be identified. A family history might be all that is required to initiate statin therapy if measuring is unavailable. Yet it is blood pressure that stands out as the most easily measured and easily treated global risk factor that should be addressed first.

This is a paper that every cardiologist should read. Of course our own work is important. Our own patients demand and should receive the best possible care. What Lopez and his colleagues have shown is a no-holds-barred description of where the real burdens of illness exist in the world. We might put a little more in the collection plate at church tomorrow. I certainly will.

Coretta King, American civil rights activist and wife of Martin Luther King, Jr, dies; Al Jazeera launches Al Jazeera English, its English language news channel for a rapidly growing audience; and the Chinese River Dolphin, or Baijitun, becomes extinct.
Optimal medical therapy with or without PCI for stable coronary disease

W. E. Boden, R. A. O’Rourke, K. K. Teo, P. M. Hartigan, D. J. Maron, W. J. Kostuk, M. Knudtson, M. Dada, P. Casperson, C. L. Harris, et al; COURAGE Trial Research Group


The COURAGE trial (Clinical Outcomes Utilizing Revascularization and Aggressive drug Evaluation) continues to resonate around the cardiology world, 5 years after its publication. This is a status that few studies have ever achieved. Boden’s groundbreaking work turned the cardiology world on its head, particularly the dominance of interventional cardiology. A few years ago cardiologists were kings of the castle and angioplasty could do no wrong. It was widely held through the 1990s and early 2000s that coronary angioplasty and stent insertion would offer sustained and important benefits, protecting the individual from heart attack, heart failure, and death.

In the late 1900s when the COURAGE trial was being designed, there was near-universal public opinion that angioplasty was good for you, a view supported strongly and strengthened by leading practitioners in coronary interventional cardiology. With COURAGE, Bill Boden and colleagues showed that the protective benefits of angioplasty were a myth.

COURAGE was well titled, since this was clearly a crucial trial to undertake, and a brave one. When COURAGE was published, there was quiet consternation in the angioplasty world. Yet although there was much discussion, there was no rejection of Bowden’s findings. The trial was very large, extremely well conducted, and the findings were incontrovertible: medical therapy was every bit as good at preventing heart attack as angioplasty.

The findings became quickly accepted in the cardiology world: angioplasty offered an important relief of symptoms, but prevention of heart attack depended on aggressive treatment of risk factors. So in a way, one of the key outcomes from COURAGE was the importance of treating hypertension and dyslipidemia to the most aggressive achievable means, and that reliance on stent insertion would not protect the individual.

Boden encompasses a great swathe of cardiology with the sentence, “… unstable coronary lesions that lead to myocardial infarction are not necessarily severely stenotic, and severely stenotic lesions are not necessarily unstable.” This single sentence epitomizes our present understanding, that plaque stabilization is the key to long-term cardiovascular protection. While this belief was not new at the time of publication, it was not widespread, and the crucial value of COURAGE was to drive the importance of risk factor modification into the minds of every practicing cardiologist, whether interventionalist or not.

Millions of angioplasty and stent insertions are still carried out each year, and angioplasty is of course a valuable and safe procedure for the relief of angina. But there has been a noticeable change in the last 5 years in the discharge summaries written by interventionalists. The final paragraph always now includes the importance of aggressive risk factor modification, with low cholesterol and blood pressure, life-style change and diet, as central and paramount to continued good health of the individual. Boden’s COURAGE trial deserves to stand with the cornerstones of cardiology research, for example Davies’ 1984 paper on plaque rupture, Petersen’s 4S trial, Shepherd’s WOSCOPS (West of Scotland Coronary Prevention Study), GISSI-1 (Gruppo Italiano per lo Studio della Streptochinasi nell’Infarto miocardico) and ISIS-2 (Second International Study of Infarct Survival); and Swedberg’s CONSENSUS (COoperative North Scandinavian ENalapril SUrvival Study), as trials of medical therapy that have transformed medical practice.

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**2007**

*Casino Royale*, starring Daniel Craig, is Best Film at the 12th Empire Awards; Helen Mirren wins 2007 Academy Award for Best Actress for her role as Queen Elizabeth II in *The Queen*; and Eddy Murphy is Worst Actor at the 28th Golden Raspberry Awards, for his role in *Norbit*: the film was a commercial success.
Writing in 2011, it seems surprising that the contribution of heart rate to cardiovascular risk is a new concept. Yet it is one worth examining, and Fox's seminal paper in 2007 has many notable and particular features, not least the fact that Fox persuaded so many leading European and American heavyweights of cardiology to join him in this review. This in itself makes the paper worth reading.

This monograph crystallizes what many cardiologists already believe. We have all grown up with the understanding of angina as the symptom of chest pain caused by myocardial ischemia, brought on by excessive cardiac work. Cardiac work can be measured as a product of blood pressure and heart rate, yet this fundamental cornerstone of cardiology has often been given little or no consideration in the guidelines for coronary artery disease, even those written in recent years.

It is remarkably far-sighted of this review, that it came before the current major trials of heart rate–reducing agents in heart failure, which have changed clinical practice. Cardiologists are well aware of heart rate and angina, and the article summarizes the epidemiological association between heart rate and outcome with an abundance of persuasive data from epidemiologic surveys and clinical trials. For example, Fox examines the β-blocker data, and the strong suggestion is that, while other mechanisms may be involved, the reduction of heart rate itself is important.

Particularly interesting is Figure 5, the reduction in heart rate in the CONSENSUS trial (COoperative North Scandinavian ENalapril SUrvival Study). I thought I had read almost everything about angiotensin-converting enzyme (ACE) inhibitors, but in 2011, Nature published a paper showing that ACE inhibitors reduce mitochondrial oxygen consumption. This fits well with a reduction in heart rate and may partly explain why ACE inhibitors are more beneficial than other vasodilators for patients with heart failure, an explanation that I always found difficult to fully explain by neuroendocrine mechanisms.

LOWEr IS BETTER FOR HEART RATE AS WELL AS BLOOD PRESSURE

Fox et al strongly suggest that a high heart rate is bad for you and the data certainly support this. There are certainly old data in the literature about relaxation therapy and angina. Fox et al’s article reminds us of the importance of making time for relaxation in our lives so dominated by deadlines, e-mails, and clinics.

In a way, the article is remarkable in that it predicts what was to be seen over the next few years in heart failure studies, which subsequently have influenced European Guidelines, resulting in better care for our patients.

When this paper was published, it reinforced my beliefs in heart rate reduction as a treatment for angina, a concept drilled into me by Attilio Maseri at the Hammersmith Hospital in London in 1990. More than 20 years later, Maseri’s lessons are well learned, and his predictions from so many years ago have come true.

The 3rd International Polar Year (IPY) starts, launching an ambitious Arctic climate change research project in Canada; the Scout movement, founded by Lieutenant General Robert Baden-Powell, celebrates its 100th anniversary; and German composer Karlheinz Stockhausen (known, inter alia, for his Helikopter-Streichquartett, for string quartet and four helicopters) dies of sudden heart failure, aged 79.
Heart rate in the pathophysiology of coronary blood flow and myocardial ischaemia: benefit from selective bradycardic agents

G. Heusch


How do $\beta$-blockers work? Is slowing the heart rate important? These are questions we often ask our medical students. Such drugs improve angina by reducing heart rate, and thereby reduce myocardial oxygen consumption. This is an axiom of medicine and it is timely to reexamine the physiology and mechanisms that link heart rate and ischemia.

Heusch returns to the classic experiments conducted in the 1970s and 1980s, which defined coronary blood flow mechanisms and the regulation of microvascular coronary blood flow. Heusch reminds us of physiology often overlooked nowadays, that coronary blood flow is not just supply and demand, but more an understanding of perfusion–contraction matching. That is, oxygen extraction by myocardium is near maximal, and the contraction of an area of myocardium is directly proportional to the availability of oxygen. Heusch describes the classic experiments showing that autoregulation occurs with blood pressures between 50 and 130 mm Hg. This is now becoming clinically apparent with re-evaluation of blood pressure in the major trials in hypertension and acute coronary syndromes. There is a marked increase in cardiovascular events among coronary patients where diastolic blood pressure is lower than about 60 mm Hg. This is the J-shaped curve of hypertension. There have been a number of recent publications, led notably by Franz Messerli in New York, posing important questions about over-aggressive blood pressure lowering in patients with coronary heart disease.

Heusch’s descriptions of coronary flow and heart rate remind us of the phenomenon often seen in the cath lab. Coronary perfusion occurs only during diastole, since during systole, the coronary arteries are squeezed by the contracting myocardium. Thus with high heart rates, coronary perfusion is markedly reduced. This has been observed by interventionists for many years.

A further perspective that Heusch introduces is the deleterious effect of $\beta$-blockers, allowing endogenous stimulation of $\alpha$-adrenergic receptors by local and circulating norepinephrine. This experimental feature helps to explain why $\beta$-blockers are perhaps not as good as they should be, as is so well demonstrated in the ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) hypertension trial. We now know from the very large trials of ivabradine that additional heart rate lowering on top of $\beta$-blockade provides substantial and sustained benefit. Ivabradine provides heart rate reduction without $\alpha$-adrenergic stimulation and this may be one crucial mechanism as part of the benefit of ivabradine in coronary disease. Moreover, Heusch reminds us that $\beta$-blockers cause impairment of isovolumic ventricular relaxation, that is, the gradual loss of intramyocardial tension that occurs in early diastole to promote coronary blood flow. In theory at least, ivabradine should offer significant benefits over $\beta$-blockers.

An interesting clinical trial would be one where patients with hypertension and angina are randomized either to $\beta$-blockade or to an ivabradine–angiotensin-converting enzyme (ACE) inhibitor combination. $\beta$-Blockers principally lower blood pressure by reduction in renin release from the kidney, and ACE inhibitors work mainly by blocking conversion of angiotensin I to II in the circulation and vascular wall. Heart rates could be matched between the $\beta$-blocker and the ivabradine group, and blood pressure likewise by titration of the ACE inhibitor. To my knowledge, this has not been undertaken, but would be a most appealing study to conduct. What Heusch’s paper does is to prepare the way and explain the science behind the forthcoming landmark clinical trials of heart rate lowering with ivabradine.

French author Alain Robbe-Grillet, one of the founders of the *Nouveau Roman*, dies, aged 86; French author Jean-Marie Gustave Le Clézio wins Nobel Prize in Literature; and Swiss oceanographer and engineer Jacques Piccard, inventor of the bathyscaphe, dies, aged 86.
new drugs for angina are uncommon. We have had nitrates for about 100 years; β-blockers for nearly 50 years; and calcium channel blockers for about 30 years. So the results of the BEAUTIFUL trial (mortality-morbidity Evaluation of the If inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction) were eagerly awaited. So what does BEAUTIFUL tell us?

First and foremost, BEAUTIFUL shows that ivabradine is a safe and effective treatment for coronary patients, demonstrated in a very large, very well-conducted study of coronary patients with left ventricular systolic dysfunction (LVSD). There was a large reduction in myocardial infarction (MI) as well as in coronary intervention in patients with heart rate (HR) ≥70. This was on top of optimal medical therapy including β-blockers prescribed for most of the trial patients. We know from the mechanism of action of ivabradine that reduction in the activity of the If channels in the sinoatrial node will be most effective at higher HR, since the action of the If current itself is less pronounced in bradycardia. Indeed, this is a safety feature of the drug, one that is less often discussed. Complete blockade of the If channel does not cause severe bradyarrhythmias, since other depolarizing channels persist, and this makes ivabradine much safer than β-blockers if patients accidently overdose their drug.

Thus, the main positive findings of the BEAUTIFUL trial are readily explained, confirming preclinical and basic science studies that showed a reduction in MI with ivabradine. MI is of course caused by plaque rupture and the theory has been held for some years that HR reduction could reduce this most catastrophic of events, and there are extensive animal data to support this.

To me, therefore, the key finding from BEAUTIFUL is that ivabradine offers real benefits to patients with ischemic heart disease and LVSD who maintain a high HR. They are almost certainly at much higher risk than patients with well-controlled HR, and for these individuals with a HR ≥70, ivabradine will offer solid and sustained benefits. Since the publication of BEAUTIFUL, this precise question has been addressed in SHIFT (Systolic Heart failure treatment with the If inhibitor ivabradine Trial). This trial, presented by Karl Swedberg just over a year ago, involved 6500 patients with severe heart failure and HR ≥70 despite optimal therapy including β-blockers. SHIFT showed a significant and sustained benefit, with reductions in heart failure hospitalizations and heart failure deaths. It has been suggested that the β-blocker doses used were ineffective, yet in the real world, few patients can tolerate the maximum dose of β-blockers suggested for heart failure patients. The doses achieved in the SHIFT trial were in fact larger than doses usually prescribed, identified by surveys of clinical practice in heart failure. Finally, and most importantly for patients with heart failure, McAlister, publishing in 2009 in the Annals of Internal Medicine a meta-analysis of 19 000 patients, showed that the benefits of β-blockers in heart failure were related to the degree of heart rate lowering, not to the dose of β-blocker used. This, then is clear evidence that HR reduction is crucial and central to the benefits of both β-blockers and ivabradine in heart failure, and fits exactly with the predictions from animal and preclinical studies.

So, in conclusion, what have we learned from BEAUTIFUL 4 years on? With hindsight, BEAUTIFUL achieved exactly what it should have done, with our greater knowledge of ivabradine in 2011. Ivabradine in BEAUTIFUL was very effective for prevention of coronary events and had a powerful protective benefit for patients with higher heart rates. This has been borne out by further major trial data.

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Large trials in angina patients are few and far between nowadays. Most of these large studies were carried out in the 1990s and earlier. Indeed the only true landmark angina trial in the last 15 years was the publication of the TIBET trial (Total Ischaemic Burden European Trial) by Kim Fox and colleagues. TIBET examined atenolol, nifedipine, and their combination in patients with mild angina and found little to choose between the groups.

More recently, and particularly with the publication of the COURAGE trial (Clinical Outcomes Utilizing Revascularization and AGgressive drug Evaluation) in 2007 the focus has been on combination therapy for patients with stable angina, much as the treatment of hypertension now rests on combination therapy rather than large doses of a single agent. The real value of the ASSOCIATE study (evaluation of the Antianginal efficacy and Safety of the aSsociation Of the If Current Inhibitor ivabradine w ith a beTa-blockEr) is that the trial examined the benefits of adding ivabradine—a new drug with excellent safety profile and emerging value in heart failure—to the mainstay drug for patients with angina, atenolol. The most widespread dose of atenolol used in clinical practice is 50 mg/day and this was chosen for the study. Purists might insist on 100 mg/day, but the reality in clinic is that such a high dose is frequently associated with side effects of fatigue, cold peripheries, nocturnal disturbances, and erectile dysfunction. What ASSOCIATE shows is that patients on the ivabradine-atenolol combination exercised for almost half a minute longer during the third stage of the Bruce protocol. During the third stage, the individual is walking briskly up a steep hill with a 14% gradient. To achieve almost an additional half minute of exercise is a substantial increase in exercise capacity. This would certainly be noticed by patients in their usual daily activity, and the ASSOCIATE trial results also showed corresponding improvements in measurements of exercise-related ischemia. Thus, in real world terms, for stable patients with angina and ischemia, the addition of ivabradine offers important benefits, even when patients are fairly well controlled to start with. To put this trial in context, this is the first trial to show real changes in angina and ischemia when drugs are added to background therapy with atenolol. Although we all routinely add calcium channel blockers and nitrates to patients already on a β-blocker, ASSOCIATE is in fact the only substantial evidence that benefits can be predicted. This is an important finding, and makes a valuable contribution to the literature on angina management.

So is ASSOCIATE a landmark study? The gravitas and long-term value of clinical trials usually evolve over several years. For example, TIBET is a landmark trial, even though the results showed equivalence. BEAUTIFUL (morBidity-mortality EvAluaTion of the If inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction) and SHIFT will become landmark trials, since they point the way to the future for an important class of new drugs. ASSOCIATE will be spoken of under the umbrella of the If channel blocker evidence database for providing the truth about improved treatment of angina, ischemia, and heart failure.

The combination of BEAUTIFUL, SHIFT, and ASSOCIATE gives us the comfort of studies involving 18 000 patients. In the triumvirate of safety, efficacy, and outcome, ivabradine ticks all the boxes and ASSOCIATE will be worth its prominent place in the literature.

Efficacy of the If current inhibitor ivabradine in patients with chronic stable angina receiving beta-blocker therapy: a 4-month, randomized, placebo-controlled trial

J. C. Tardif, P. Ponikowski, T. Kahan; ASSOCIATE Study Investigators

*Eur Heart J.* 2009;30:540-548

As a consequence of the US subprime mortgage crisis, the Icelandic banking system collapses; longest total solar eclipse (6 minutes and 38.8 seconds) of the 21st century, visible over parts of Asia and the Pacific Ocean; and Greenlandic, related to Inuit and spoken by about 57 000 people, replaces Danish as the official language of Greenland
Cardiovascular research and the new biology of genetics, stem cells, recombinant therapy, and virus-delivered alteration of an individual's DNA has thunderous appeal, yet remains elusively beyond our reach. Billions of dollars have been poured into genetic research, trying to identify genes responsible for the common manifestations of hypertension, atheroma, and coronary disease. Yet, the contributions made by gene research have not shown any real widespread clinical benefit yet.

Zachary and Morgan concentrate on the focused area of angiogenesis. The development of new blood vessels for ischemic tissue is a biological process fundamental to organic life. Angiogenesis is of course central to growth and development, but in disease states, for example, diabetic eye disease, neovascularization is unwelcome and leads to severe disability. Yet, can these same processes be encouraged to promote new blood vessel formation in ischemic limbs or ischemic myocardium, without detriment to other tissues and organs?

The authors show us that the data from animal models are encouraging, yet clinical studies are uniformly disappointing. This of course is familiar in translational medicine. Research in angiogenesis reminds us of the biochemical pathways we all studied as students, but multiplied 100-fold, as the interactions between cytokines, the endocrine and paracrine systems, and a host of local factors that we do not readily understand, have complex interactions and backups processes that we are only beginning to interpret. It must be remembered that these processes have evolved over millions of years, to enable organ growth and to construct defense mechanisms. For example, nitric oxide biology was thought to explain a large part of vascular physiology. Philip Poole-Wilson and I showed almost 20 years ago that the heart failure of septic shock could be reversed by blockade of nitric oxide. Others showed that hypertension could be substantially reversed, heart failure improved and a host of other cardiovascular conditions could be modified successfully in experimental models of nitric oxide biology. Yet none of these has worked in clinical practice apart from nitrates for angina and angiotensin-converting enzyme inhibitors in heart failure, a sobering reminder that we have evolved redundancy and duplication, with numerous pathways performing the same function, to preserve the integrity of the individual. Maseri's landmark study with blockade of nitric oxide in the human coronary arteries showed remarkably little effect on coronary blood flow, a study carried out more than 20 years ago. So it is not surprising that any expectation of major benefit by injection of an angiogenic growth factor would be optimistic.

What Zachary and Morgan really tell us is that while we understand some of the processes involved in angiogenesis, we have not yet grasped fully the local tissue interactions that regulate blood flow. It seems logical to believe that angiogenic signals must be generated locally and in a sustained fashion. The challenge will be to deliver or stimulate the signal with enough time for local blood vessels to develop. Vascular neogenesis in the eye takes months or years, and the belief that a simple application of a growth factor might result in better blood supply is specious and simplistic. Yet, the experimental models are encouraging and so the search goes on. On the simplest level, we do not understand why some patients with apparently similar patterns of coronary or peripheral vascular disease develop markedly different degrees of ischemia or infarction. Much remains to be learned.

President Zine El Abidine Ben Ali of Tunisia flees to Saudi Arabia after 23 years in power, the first leader to fall to the Arab Spring; Hosni Mubarak, Egyptian President since 1981, is ousted after 18 days of demonstrations in Tahrir Square, in Cairo; and Libyan leader Muammar Gaddafi is killed after nine months of demonstrations and civil war in Libya, ending a 42-year-long rule.
Intramyocardial, autologous CD34+ cell therapy for refractory angina


Let us hope fervently that in 20 years' time we can look back at the publication of the paper of Losordo et al in 2011 as one of the fundamental and most influential studies of modern cardiovascular biology. We have evolved with numerous wound repair and cellular repair mechanisms. Among the most active repair and replacement systems is the bone marrow where hematopoietic stem cells, known as CD34+ cells, can differentiate to produce white blood cells, red blood cells, and megakaryocytes. The relative ease of obtaining these cells has been greatly enhanced by techniques of CD34+ cell amplification using appropriate stimuli to the bone marrow, principally granulocyte colony-stimulating factor (G-CSF). This technique to generate large numbers of hematopoietic stems has been used by hematologists for some time, but Losordo and his colleagues were the first to use this technique in a sizeable clinical study for patients with refractory ischemia.

Previous studies of stem cells in refractory ischemia had tried intracoronary infusion of cells, in the hope that the cells would stick somehow in the blood vessels that supplied ischemic territory. It is much more likely that these cells were washed through the coronary circulation and lost to the periphery. The approach that Losordo took was to use a percutaneous coronary injection system where the myocardium could be directly punctured from the coronary arteries, with local delivery of CD34+ cells into ischemic tissue. This is rather akin to growing plants. Seeds germinate much better when placed in a trench and covered with soil, rather than scattered optimistically on the ground. By mechanisms that are not yet fully understood, CD34+ cells stimulate growth of new blood vessels in ischemic tissue. Whether this is by recruitment of local angiogenic factors or stimulation of local processes is not yet understood. It seems unlikely that differentiation of CD34+ cells into blood vessels is the mechanism, since insufficient cells could be delivered in a suitable matrix for vascular degeneration.

What Losordo et al really show is the safety of intramyocardial injection, with the suggestion and promise of improvement. Really, this study is a proof of concept that local delivery of stem cells can be achieved. Simple coronary infusion of cells has not been successful, and this study is the first description of the injection technique in a substantial number of patients to see whether the procedure is safe, and then whether it is effective. As with many medical devices, for example the earliest pacemakers and intracoronary stents, injection technology might look obsolete when viewed from the year 2030. Yet the pioneers of pacemakers and stents are now rightly hailed as physician-scientists who have made great contributions.

Losordo et al’s description of these early steps to promote myocardial neovascularization represents a possible giant step forward in cardiovascular therapeutics. CD34+ cells are readily obtained from peripheral blood without the need for painful and complicated bone marrow sampling. The technology of stimulating amplification of these cells is now well understood and a much larger phase 3 clinical trial is due to start shortly. Let us hope that we can look back to the years around 2012 to 2014 saying, “that was the time we introduced new drugs to replace warfarin, and that was the time that autologous stem cell injection became feasible.”

Losordo et al’s study is the first to show real hope for autologous stem cells in the heart and we await the major trials with great interest and excitement.

NASA concludes its space shuttle program after Atlantis successfully lands at Kennedy Space Center on 21st July; Al-Qaeda founder and leader Osama bin Laden is killed during an American military operation in Pakistan; and worst-ever floods paralyze Thailand, affecting 58 of the country’s 77 provinces and killing 283
Angina: Old Concepts Revisited

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selected by Jeffrey S. Borer, MD
Division of Cardiovascular Medicine - Department of Medicine; Cardiovascular Translational Research Institute
State University of New York - Downstate Medical Center and College of Medicine - Brooklyn and New York - NY - USA
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