Stable Angina and $I_f$ Inhibition: New Insights and Applications

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A new treatment approach for patients with stable angina: selective and specific $I_f$ inhibition

by M. Tendera, Poland

The prevalence of ischemic heart disease is still high. Despite an important reduction in mortality, mainly as a result of improved primary and secondary prevention, there are still important unmet needs to be satisfied in the treatment of the disease. New pharmacological agents are needed to alleviate the symptoms, improve exercise tolerance, and improve quality of life. In this context, the novel selective and specific $I_f$ inhibitor ivabradine has been shown to provide effective and safe treatment of stable angina through exclusive heart rate reduction.

Magnitude of the problem

Over the last two decades, age-adjusted mortality due to coronary artery disease has decreased in most European countries. This is a consequence of better treatment and improved survival in patients having experienced acute coronary events, and lower incidence of the disease, especially among younger people, resulting from more effective primary and secondary prevention of atherosclerosis. The absolute number of coronary events remains relatively constant. This means that in practice the burden of coronary atherosclerosis has shifted to older age groups. Ischemic heart disease remains the leading cause of mortality and morbidity and continues to be a major burden to public health. The true prevalence of chronic ischemic heart disease is difficult to estimate, since symptoms may not be typical and their predictive value for ischemia depends on sex and age, and—in the other hand—myocardial ischemia is not necessarily symptomatic.

Stable angina pectoris, which is a common manifestation of ischemia, is widely used to estimate the prevalence of ischemic heart disease. Angina occurs more frequently in men. Its prevalence increases with age in both sexes, from 2% to 5% in men aged 45 to 54 years, to 11% to 20% in those aged 65 to 74 years. In women, respective values increase from 0.5% to 1% to 10% to 14%. Above age 75, the prevalence of angina in men and women is almost equal. It is estimated that in countries with high ischemic heart disease rates the total number of persons with angina may be as high as 30 to 40 thousand per million total population. In a substantial proportion of patients, angina causes an important limitation of everyday activities and impairs quality of life. Thus, stable angina pectoris is common and may be debilitating.

Mortality in patients with stable angina is estimated at 2% to 3% per year. This means that in the majority of patients risk of death may be only moderately increased as compared with age-matched healthy subjects. However, prognosis in patients with chronic angina is not uniform. It depends on several factors, including underlying coronary anatomy, left ventricular function, and comorbidities. Identification of high-risk patients who can benefit from therapy aimed to improve prognosis is of utmost importance. In low-risk patients, the main aim of treatment is to eliminate symptoms and improve health-related quality of life.
Treatment options
Introduction of surgical and percutaneous myocardial revascularization has dramatically changed the treatment of patients with ischemic heart disease. Revascularization offers effective relief of symptoms, and in patients with extensive ischemia, like those with left main or three-vessel disease, also improves prognosis. Effective restoration of adequate coronary flow, either surgical or percutaneous, does not obviate the need for medical treatment. Medical therapy is necessary to prevent subsequent events and to treat residual or recurrent ischemia. In addition, not all patients with chronic ischemia require revascularization. Medical treatment is still recommended as first-line strategy to control symptoms.2

β-Blockers, calcium channel blocking agents, and nitrates have been the mainstay of medical therapy of chronic angina for a long time. Although these drugs can also improve oxygen supply, they predominantly act by decreasing myocardial oxygen demand. Contractility, systolic wall tension, and heart rate are the most important determinants of oxygen demand. Heart rate is relatively easy to change, and therefore its reduction is often targeted. In the presence of ischemia, heart rate reduction may restore the balance between myocardial oxygen supply and demand. Slowing of heart rate not only decreases oxygen demand, but also improves myocardial perfusion through prolongation of diastole. β-Blockers and some calcium channel blockers act, at least in part, through this mechanism. β-Blockers are most often recommended as primary therapy since, in addition to symptomatic relief, they have been found to reduce mortality and reinfarction, at least in postinfarction patients.5 Heart rate is often used to determine the appropriate dosage of β-blockers. The recommended target heart rate on treatment is in the range of 55 to 60 per minute at rest, and around 75% of that which provokes ischemia on exercise.6 In clinical practice this target is often not reached because of adverse effects: fatigue, lethargy, insomnia, worsening claudication, or erectile dysfunction in men. In addition, β-blockers are contraindicated in some patients, including those with reversible airways obstruction, atrioventricular conduction defects, decompensated heart failure, symptomatic peripheral vascular disease, brittle diabetes, or history of severe depression.

Some calcium channel blockers, like verapamil or diltiazem, can also slow the heart rate, but their effect is difficult to predict, and the data on their clinical benefit are rather scanty. Therefore, there is an evident need for another class of drugs that could attain this effect administered alone or on the top of other agents.

The concept of If current blockade
The pacemaker (If) current plays a central role in heart rate control.7 This makes it an interesting target for pharmacological intervention. Inhibition of the If current results in heart rate reduction, with no other effects on the heart. This bradycardic effect has a clear potential to reduce ischemia.

Ivabradine is a selective and specific If current blocker8,9 that has been used to test this novel therapeutic concept. As opposed to β-blockers, ivabradine has no negative inotropic action. It also has no impact on atrioventricular nodal conduction. In an experimental model, it decreased exercise-induced ECG changes to the same extent as propranolol, but was able to better preserve systolic function in the ischemic area.10 Ivabradine was also shown to be superior to β-blockade in the setting of myocardial stunning, where it improved contractility.11 In humans, ivabradine significantly slows heart rate at rest and at peak exercise.12 It has been shown to be a safe and effective antianginal and anti-ischemic agent in patients with stable angina. In a double-blind placebo-controlled study, it produced a dose-dependent prolongation of total exercise time and time to development of ischemia.12

Heart rate reduction with ivabradine may carry additional benefits beyond relief of angina and ischemia. Animal studies show that slow heart rate may attenuate the development of atherosclerosis.13 Long-term administration of ivabradine is associated with improvement in left ventricular function in rats with induced myocardial infarction.14 In humans, lower heart rates may reduce the odds of plaque rupture and thus the probability of a new acute coronary event.15,16

The novel concept of treatment of chronic ischemic heart disease with the If current blocker ivabradine has proved effective in patients with angina, and holds promise in other patient groups, like those at high risk of acute coronary events or those with compromised left ventricular systolic function.
Une nouvelle approche thérapeutique dans le traitement de l’angor stable: l’inhibition selective et spécifique du courant If
rosclérose. Le nombre absolu des événements coronaires reste cependant relativement constant, ce qui veut dire, qu’en pratique, le fardeau de l’athérosclérose coronaire n’a fait que se déplacer vers les sujets plus âgés. Les cardiopathies ischémiques restent la principale cause de mortalité et de morbidité. Elles continuent de peser lourdement en santé publique. La prévalence exacte des cardiopathies ischémiques chroniques est difficile à estimer, car leurs symptômes ne sont pas toujours typiques et la valeur prédictive de ceux-ci quant à l’existence d’une ischémie myocardique dépend du sexe et de l’âge. Cette dernière, d’autre part, n’est pas nécessairement associée à des symptômes.

L’angor stable, manifestation courante de l’ischémie, est généralement utilisé pour estimer la prévalence des cardiopathies ischémiques. Ce symptôme survient plus souvent chez l’homme. Sa prévalence augmente avec l’âge dans les deux sexes. Elle est de 2-5 % chez l’homme âgé de 45 à 54 ans et de 11-20 % entre 65 et 74 ans. Chez la femme, les valeurs correspondantes sont respectivement de 0,5-1,0 % et de 10-14 %. Après 75 ans, la prévalence de l’angor dans les deux sexes est à peine égale 2. On estime que, dans les pays où les cardiopathies ischémiques sont courantes, le nombre total de sujets atteints d’un angor peut atteindre 30000 à 40000 par million d’habitants 2. Dans une proportion substantielle de cas, l’angor est à l’origine d’une limitation importante des activités quotidiennes et retentit sur la qualité de vie. Ce symptôme, qui est donc commun, peut être débilitant.

La mortalité en cas d’angor stable est estimée à 2-3 % par an 2. En d’autres termes, par rapport à des sujets sains appariés selon l’âge, le risque de décès, chez la majorité des malades, ne semble que modérément augmenté. Cependant, le pronostic de l’angor stable est loin d’être uniforme. Il dépend en fait de nombreux facteurs, dont l’anatomie coronaire, la fonction ventriculaire gauche et les comorbidités. L’identification des malades à haut risque qui vont bénéficier le plus des traitements destinés à améliorer le pronostic est donc de la plus haute importance. Chez les malades à faible risque, l’objectif principal du traitement est de soulager les symptômes et d’améliorer la qualité de vie dépendant de la santé.

Options thérapeutiques
L’introduction de la revascularisation chirurgicale et percutanée a profondément modifié la prise en charge thérapeutique des cardiopathies ischémiques. La revascularisation soulage efficacement les symptômes et, en cas d’ischémie étendue, liée, par exemple, à une atteinte du tronc de l’artère coronaire gauche ou à des lésions tritronculaires, elle améliore aussi le pronostic. La restauration effective d’un débit sanguin coronaire approprié, que ce soit par voie percutanée ou chirurgicale, ne dispense pas du traitement médical. Celui-ci reste nécessaire pour prévenir les événements ultérieurs et traiter l’ischémie résiduelle ou récidivante. De plus, tous les malades atteints d’une ischémie chronique ne sont pas justiciables d’une revascularisation. Le traitement médical est encore recommandé en tant que stratégie thérapeutique de première intention pour contrôler les symptômes 2.

Les bétabloquants, les inhibiteurs calciques et les dérivés nitrés ont longtemps été les piliers du traitement médical de l’angor stable. Ces médicaments agissent principalement en diminuant les besoins myocardiques en oxygène, bien qu’ils soient capables d’augmenter les apports de ce dernier. La contractilité, la tension pariétale systolique et la fréquence cardiaque sont les principaux déterminants des besoins myocardiques en oxygène. La fréquence cardiaque est relativement facile à modifier, et, de ce fait, sa réduction est souvent ciblée. En présence d’une ischémie, la baisse de la fréquence cardiaque peut restaurer l’équilibre entre les apports et les besoins en oxygène. Le ralentissement de la fréquence cardiaque diminue certes les besoins en O2, mais il améliore aussi la perfusion myocardique en prolongeant la diastole. Les bétabloquants et certains inhibiteurs calciques agissent, au moins en partie, selon ce mécanisme. Les bétabloquants sont le plus souvent recommandés en première intention, car, en plus de leur effet symptomatique, ils sont capables de réduire la mortalité et la fréquence des infarctus récidivants, tout au moins dans le postinfarctus 5. La fréquence cardiaque est souvent utilisée pour choisir le dosage le plus approprié de bétabloquants. Elle peut se situer entre 55 et 60 par minute au repos et autour de 75 % de la fréquence qui provoque une ischémie à l’effort 6. En pratique courante, cet objectif n’est souvent pas atteint, du fait des effets indésirables : asthénie, létargie, insomnie, aggravation d’une claudication intermittente ou dysfonctionnement érectile chez l’homme. De plus, les bétabloquants sont contre-indiqués chez certains malades, notamment ceux atteints d’un bronchospasme réversible, de troubles de la conduction auriculoventriculaire, d’une insuffisance cardiaque décompensée, d’une artériopathie périphérique symptomatique, d’un diabète difficile à équilibrer ou encore en cas d’antécédents de dépression sévère.
Certains inhibiteurs calciques, tels le vérapamil ou le diltiazem, peuvent aussi ralentir la fréquence cardiaque, mais il est difficile de prédire leur effet, et, de plus, leur bénéfice clinique est plutôt mal documenté. De fait, il y a besoin à l’évidence d’une autre classe thérapeutique qui pourrait atteindre un tel effet, que le médicament soit administré seul ou en plus des autres agents.

**Le concept d’inhibition du courant \( I_f \)**

Le courant pacemaker (\( I_f \)) joue un rôle central dans le contrôle de la fréquence cardiaque. De ce fait, il constitue une cible privilégiée pour les interventions pharmacologiques. L’inhibition du courant \( I_f \) entraîne une diminution de la fréquence cardiaque qui ne s’accompagne d’aucun autre effet sur le cœur. Cet effet bradycardisant permet potentiellement de réduire l’ischémie.

L’ivabradine est un inhibiteur sélectif et spécifique du courant \( I_f \) et a été utilisé à ce titre pour tester ce nouveau concept thérapeutique. À la différence des bétabloquants, l’ivabradine n’exerce pas d’effet inotrope négatif. Elle n’a pas non plus d’impact sur la conduction nodale auriculoventriculaire. Dans un modèle expérimental, elle est capable de diminuer les anomalies électrocardiographiques induites par l’effort, comme le fait le propranolol, mais, à la différence de celui-ci, elle permet de mieux préserver la fonction systolique dans les régions ischémiques. L’ivabradine s’est également révélée supérieure aux bétabloquants dans le contexte de la sidération myocardique où elle est capable d’améliorer la contractilité. Chez l’homme, l’ivabradine ralentit significativement la fréquence cardiaque au repos comme à l’effort maximal. Elle a fait la preuve de son activité antiangineuse et anti-ischémique, mais aussi de sa bonne tolérance chez les malades atteints d’un angor stable. Dans une étude contrôlée, menée à double insu contre placebo, l’ivabradine a permis d’obtenir un allongement dose-dépendant de la durée totale de l’effort et du délai avant la survenue d’une ischémie.

La réduction de la fréquence cardiaque obtenue grâce à l’ivabradine peut apporter un bénéfice additionnel qui va au-delà du soulagement de l’angor et de l’ischémie. Les études réalisées chez l’animal montrent que le ralentissement de la fréquence cardiaque permet d’atténuer le développement de l’athérosclérose. L’administration de l’ivabradine au long cours s’associe à une amélioration de la fonction ventriculaire gauche chez les rats atteints d’un infarctus du myocarde expérimental. Chez l’homme, des fréquences cardiaques plus lentes pourraient réduire le risque de rupture de plaque et ainsi la probabilité d’un nouvel événement coronarien aigu.

L’ivabradine, au travers de l’inhibition du courant \( I_f \), inaugure un concept thérapeutique nouveau dans la prise en charge des cardiopathies ischémiques. Ce médicament a fait la preuve de son efficacité chez les malades atteints d’angor. Il s’annonce prometteur dans d’autres groupes de patients, notamment chez ceux ayant un risque élevé de syndrome coronarien aigu ou atteints d’une altération de la fonction systolique ventriculaire gauche.
Coronary atherosclerosis most commonly presents in the community as angina pectoris, followed by acute coronary syndromes (acute myocardial infarction and unstable angina), and, finally, as sudden cardiac death. Atherosclerosis also affects the rest of the arterial circulation, principally the aorta and its major branches to the head and limbs. Patients presenting with cerebral ischemia or infarction, or symptoms of peripheral arterial disease, usually have coronary atherosclerosis as well. For those who survive these other clinical manifestations of atherosclerosis, the commonest cause of death is coronary heart disease (CHD).

When the acute manifestations of coronary artery disease—sudden cardiac death and acute myocardial infarction—are considered together, then 1 in 2 patients with new or recurrent disease die within 30 days of their acute clinical presentation.1-4 About 69% die in the community, 29% die in hospital, and the other 2% die within 30 days of discharge. However, when all first nonfatal and fatal symptomatic expressions of coronary atherosclerosis are considered together—angina pectoris, acute coronary syndromes, and sudden cardiac death—the vast majority of patients survive their first clinical presentation, with only up to one fifth of all such incident cases due to sudden unheralded cardiac death in the community. Therefore, considerable potential exists among those with angina and nonfatal acute coronary syndromes to reduce subsequent morbidity and mortality through therapeutic and revascularization procedures and, over the longer term, by lifestyle changes, risk factor modification, and the use of prophylactic drug therapies such as aspirin, β-blockers, angiotensin-converting enzyme (ACE) inhibitors, cholesterol modification therapy, and anticoagulation.

**Incidence of CHD**

The incidence of CHD—angina pectoris, acute coronary syndromes, and sudden cardiac death—is only available from specially conducted community surveys. The Bromley Coronary Heart Disease Register (BCHDR) is the only contemporary community register to identify all symptomatic med-
rical presentations of CHD in one population. All incident (first) presentations of exertional angina, acute coronary syndromes, and sudden cardiac death were registered for Bromley Health District in South East London (population 186,053 in men and women aged 25 to 74 years) for the period 1996 to 1998 (Figures 1 and 2). Incidence rates for exertional angina, acute coronary syndromes, and sudden cardiac death derived from this community survey are given in Table I.

Chest pain

Chest pain is common in the community, and breathlessness can be a variant symptom of angina. The incidence rate for chest pain reported for the first time by patients with no medical history of CHD to medical services (a general practitioner [GP] or an Accident and Emergency [A&E] Department) and considered by a doctor to be potentially cardiac in origin, was measured as part of the Bromley CHD register (Table II, page 10). The incidence rate (95% confidence interval [CI]) for chest pain for the age group 25 to 74 years was 481 per 100,000 per annum (480, 482); men 583 (582, 584) and women 379 (378, 380). As the incidence rate for angina in women is about half that of men (see below), chest pain is a more common complaint in this group in relation to the true incidence of coronary disease.

Incidence of angina

Angina is a symptom and therefore there is greater potential for misdiagnosis, particularly in women for whom chest pain is more commonly reported. Angina incidence rates from this register inevitably count some patients who are subsequently shown at coronary arteriography to have normal coronary arteries. Incidence will therefore be inflated by including such healthy people. However, refining the diagnosis by electrocardiography (ECG), either at rest or on exercise, will underestimate true incidence. This is because the majority of patients with angina due to coronary atherosclerosis have normal resting ECGs, and only two thirds show changes consistent with myocardial ischemia (ST-segment and/or T-wave changes) on exercise, with some false positives, particularly among women. So the true incidence of angina lies somewhere between the rate calculated for symptoms alone (regardless of ECG and other findings) and that derived for patients with symptoms, objective evidence of reversible ischemia, and coronary atherosclerosis at angiography. The age- and sex-specific incidence rates for exertional angina in patients with no history of CHD from the Bromley CHD register are shown in Table I.
Prevalence of angina pectoris

Prevalence of angina has been estimated in population surveys using a standardized questionnaire. The Health Survey for England\textsuperscript{6} used the Rose Angina Questionnaire and the overall prevalence (angina grade 1 and 2) in the population aged 16 years and over was 2.6% in men and 3.1% in women. It was higher in women than in men in all age groups except for those aged 75 and over, where 7.3% of men and 5.9% of women reported this symptom. In contrast, the overall prevalence of having ever been diagnosed by a doctor with angina was 5.3% in men (3.2% currently) and 3.9% in women (2.5% currently). In both sexes, prevalence increased with age, being negligible in those aged under 35 to almost 1 in 5 in those aged 75 and over (18.3% of men and 17.0% of women). The prevalence of angina as assessed by the Rose Angina Questionnaire showed a different pattern to reported doctor-diagnosed angina: the overall prevalence was lower than for reported doctor diagnosed angina, and women reported more symptoms than men. Also, the Rose Angina Questionnaire gave higher estimates in younger age groups and lower estimates in older age groups than self-reported prevalence. These different measures of prevalent angina can have different applications. From a clinical perspective, a doctor diagnosis is more useful because it is not just based on symptoms, but also takes account of other clinical information such as risk factors, investigations, and a specialist opinion. Angina based on hospital discharges and deaths has no meaning for the community because most patients with exertional angina are never admitted to hospital at the time they first present to medical services.

### Tables III and IV

The incidence rate for exertional angina for the age group 25 to 74 years was 122 per 100,000 per annum (105, 138). The incidence rate for men was 172 (146, 198) and for women 89 (74, 106).

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Presentation and management of cardiac chest pain in the community

A patient seeking medical advice for chest pain can do so through the GP or through the A&E Department. The doctor has to decide is the pain cardiac in origin and, if so, whether it is due to an acute coronary syndrome or exertional angina. The former requires urgent assessment in hospital whereas the latter can be managed as an outpatient. For the GP, the diagnosis can be difficult from the history alone. Options are to perform an ECG, send the patient to casualty, refer for an open access 12-lead ECG (and in some hospitals open-access exercise testing is also available), or refer for a cardiology outpatient opinion. Community surveys of angina suggest most patients with “stable angina” are managed by their GP, while only a small minority is referred for specialist opinion and investigations. For those presenting directly to casualty, the doctor can admit or refer to cardiology outpatient care or back to the GP. The consequence in casualty is that there are up to 25% inappropriate admissions of noncardiac chest pain to hospital with the label “chest pain—exclude myocardial infarction” and, conversely, between 2% and 12% of patients being inappropriately discharged from hospital who turn out to have coronary disease.7

Presentation and management of exertional angina in the community

Criteria for referring patients with exertional angina from primary care to a hospital specialist are often not defined, and therefore there is likely to be a large variation in practice between GPs. Some GPs will refer patients when they first present, whereas others will manage patients medically and only refer if symptoms cannot be adequately controlled with medication alone, or for other reasons.

In one community study of prevalent angina, most patients for whom GPs prescribed nitrates had not been investigated in detail.8,9 Only 64% had had an ECG, 7% an exercise test, and 4% a coronary angiogram. One in 5 of these patients attended a hospital medical clinic during the period of the survey, and half of these were seen by a cardiologist. In a 7-year follow-up of this group of patients, 20% were admitted urgently with chest pain (although only 14% had a confirmed myocardial infarction), and a further 15% were referred for a medical outpatient appointment because of chest pain. Thirty-nine percent of patients died during this period, of whom two thirds died from cardiovascular or unknown causes. So, at the time of this survey, most patients with suspected angina were treated by GPs without specialist help. However, this picture has been radically changed by the development of Rapid Access Chest Pain Clinics (RACPCs).7,10-12

Rapid Access Chest Pain Clinics

This new approach to the diagnosis and management of patients with exertional angina is now widely available in hospitals in the UK. For example, a RACPC in Bromley provided rapid daily assessment of patients with chest pain, which, in the opinion of the referring doctor, could be due to angina. All patients had presented with chest pain for the first time, and none had a past medical history of CHD. The RACPC was open Monday through Friday, 12 midday to 4 pm, and patients could therefore be rapidly assessed without appointment, either on the day they presented or the next working day. Patients considered by the GP to have unstable angina or an evolving myocardial infarction were referred directly to the A&E Department in the usual way. Patients with chest pain who went direct to A&E without consulting their GP, and in whom an acute coronary syndrome had been excluded, were also referred to the RACPC for assessment of angina. Patients were reviewed by a cardiologist in training and had a full history, clinical examination, resting 12-lead ECG, chest x-ray, and for those with angina or possible angina, either a treadmill exercise test (Bruce protocol) and/or a thallium scan if they were unable to use the treadmill. The results of this service are shown in Table V(a). Twenty-nine percent of patients were considered to have exertional angina and two thirds noncardiac pain. One in 20 patients had an acute coronary syndrome despite the advice to refer such patients directly to casualty. These results are almost identical to those of a RACPC at another London hospital where the patient referral criteria were almost identical.15 In the Newham RACPC, the pain had to be of recent onset (within 4 weeks) and younger people (men <30 years and women <40 years) were discouraged.

These clinics show that the diagnosis of cardiac chest pain can be resolved, those with coronary disease identified, and those with noncardiac pain appropriately reassured. The difficulty in sometimes distinguishing an acute coronary syndrome from exertional angina in the community is also illustrated by the inadvertent referral of such patients to these clinics. Before the advent of RACPCs, such patients may have been inappropriately managed in general practice and not received potential life-saving treatments. Although the majority of patients seen in the RACPC did not have cardiac pain this should not necessarily be seen as a judgment of the GP’s ability to diagnose angina. The threshold for
referral to a RACPC is likely to be lower than that for referral to cardiology outpatients and therefore more noncardiac cases will be seen.

The Bromley RACPC was set up in the context of the Bromley CHD Register and so it was possible to estimate the impact of the RACPC on the number of new diagnoses of CHD in this district. The number of new exertional angina cases increased by 57% as a result of the RACPC. This increase in the number of angina patients assessed in hospital is consistent with previous reports of a low referral rate of angina patents by GPs to a specialist. When a chest pain clinic opens there will inevitably be an increase in the number of new cases of angina identified by the cardiology service, who were not previously referred for a specialist opinion.

Unlike Bromley and Newham, the referral criteria for the chest pain clinics in Edinburgh7,10 (Table Vb) were more acute — “acute or recent onset” or “new coronary syndrome (81% unstable angina), only 26% would have been hospitalized by their GP, thus delaying admission and life-saving treatments for the majority.7

Patients with exertional angina assessed in such clinics all have specialist investigations — treadmill exercise testing, radionuclear investigations, etc. — to determine the severity of coronary artery disease and myocardial ischemia. In the Bromley clinic, 85% of patients with exertional angina went on to have an exercise test (87%) or a thallium scan (13%).

On exercise testing there was objective evidence of myocardial ischemia in 72% of patients and 74% of patients who had thallium scans had a high probability of coronary artery disease. Forty-eight percent of patients classified as high risk on the basis of exercise testing and other noninvasive investigations proceeded to coronary arteriography: 60% required revascularization either in the form of angioplasty ± stent implantation (70%) or coronary artery bypass grafting (CABG, 30%), 23% were for medical therapy only, and 17% had normal coronary angiograms. Overall, 29% of all patients presenting with exertional angina required revascularization.

Therefore, rapid assessment of chest pain through a specialized clinic has several advantages: (i) it quickly resolves the cardiac diagnosis, identifies those with angina, and reassures those with noncardiac pain; (ii) it prevents unnecessary hospital admissions with chest pain; and (iii) it risk-stratifies patients for coronary arteriography and revascularization, thus prioritizing those at highest risk for earlier intervention.

### Drug therapies and revascularization

There is no evidence from randomized controlled trials that any therapeutic drug class used to treat the symptom angina has any survival benefit. This includes nitrates, β-blockers, calcium channel blockers, and other agents. However, there is some trial evidence from those studies that included patients with angina pectoris that prophylactic aspirin and cholesterol-lowering therapy with a statin reduces the risk of subsequent morbidity and mortality and can improve survival.16-21 In contrast, revascularization of selected patients with stable exertional angina, either by coronary artery surgery or coronary angioplasty, will reduce morbidity and mortality.13-26 After initial medical/surgical management, the clinical strategy for patients presenting with exertional angina is to reduce the risk of a myocardial infarction and coronary death.

### Cardiovascular prevention and rehabilitation

Traditionally, cardiac rehabilitation has focused on supervised exercise sessions, but this is gradually evolving into comprehensive lifestyle programs — smoking cessation, healthy food choices, as well as increased physical activity — based on behavioral models of change. Risk factor management in terms of controlling blood pressure, lipids, and diabetes, and the use of prophylactic drug therapies such as

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**Table V(b). Rapid Assessment Chest Pain Clinics (RACPCs).**

<table>
<thead>
<tr>
<th>Royal Infirmary Edinburgh (n=1188)</th>
<th>Western General Edinburgh (n=278)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Referral criteria</td>
<td></td>
</tr>
<tr>
<td>Suspected cardiac chest pain of acute or recent onset and no history of CHD*</td>
<td>New or increasing chest pain, or chest pain at rest, or other chest pain of concern in patients with or without a history of CHD</td>
</tr>
<tr>
<td>Acute coronary syndromes</td>
<td></td>
</tr>
<tr>
<td>144 (12%)</td>
<td>51 (18%)</td>
</tr>
<tr>
<td>Angina</td>
<td></td>
</tr>
<tr>
<td>274 (23%)</td>
<td>89 (32%)</td>
</tr>
<tr>
<td>Noncardiac chest pain</td>
<td></td>
</tr>
<tr>
<td>768† (65%)</td>
<td>136 (49%)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (–)</td>
</tr>
</tbody>
</table>

*Patients with suspected myocardial infarction or unstable angina referred directly for hospital admission.
†Includes 82 patients with chest pain not otherwise specified.
aspirin is also becoming an integral part of this approach. And finally, the psychosocial and vocational support required to help patients lead as full a life as possible is also provided. This evolution in the scope of cardiac rehabilitation is now more appropriately called cardiovascular prevention and rehabilitation.

This evolving scope in cardiovascular prevention and rehabilitation is also embracing a broader group of coronary patients. Rehabilitation was initially offered only to patients recovering from a myocardial infarction and those who had had cardiac surgery. With the emphasis now on favorably influencing the underlying causes of the disease, patients presenting with angina are now being included after their initial medical or surgical management.

Although the evidence base for cardiovascular prevention and rehabilitation of coronary patients is now among the best of any aspect of clinical medicine, service provision still remains inadequate and this means that many coronary patients still have no access. There is also wide variation in the organization, staffing, and management of cardiac rehabilitation services. Thus, current service provision fails to meet the evidence-based guidelines for cardiac rehabilitation. Most programs are outpatient, hospital-based, concentrating on lower-risk patients who have had myocardial infarction, although many also include patients who have had coronary artery surgery or angioplasty. Women are less likely to receive cardiac rehabilitation than men. The majority of programs are still exercise-centered, although patient education on other aspects of lifestyle and CHD is provided in most. The risk factor management in patients with CHD in Europe is far from optimal. Surveys of clinical practice such as EUROASPIRE I and II (EUROper Heart Action on Prevention by Intervention to Reduce Events) have shown that integration of CHD prevention into daily practice is inadequate, and there is considerable potential to further reduce the risk in patients with established CHD because many are not achieving the recommended lifestyle and risk factor goals.

Patients with exertional angina are at high risk of progressing to an acute coronary syndrome or coronary death. By addressing lifestyle and other coronary risk factors, and by prescribing aspirin, blood pressure, and lipid-lowering therapies, the risk of disease progression can be reduced. Yet, these patients are not usually included in cardiovascular prevention and rehabilitation programs, and surveys of risk factor management like EUROASPIRE have shown that those with angina alone are least well managed compared with patients following myocardial infarction or revascularization.

**Summary**

Assessment and management of patients presenting with exertional angina in the community needs to be addressed in stages. First, prompt cardiac assessment of patients presenting for the first time with chest pain is necessary, and the model of the Rapid Access Chest Pain Clinic is one way of doing so. It quickly identifies those with angina, risk-stratifies, and prioritizes for revascularization. Second, appropriate medical and surgical management needs to follow to alleviate symptoms and reduce the risk of myocardial infarction and coronary death. Third, angina patients require comprehensive lifestyle intervention, risk factor management, and appropriate use of prophylactic drug therapies over the longer term. The object of a cardiovascular prevention and rehabilitation for angina patients is to improve both quality and length of life.

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ÉPIDÉMILOGIE DE L’ANGINE DE POITRINE

L’angine de poitrine est le tableau clinique le plus fréquent de l’athérosclérose coronaire en médecine générale. Une étude épidémiologique londonienne a rapporté une fréquence de l’angine de poitrine de 122 personnes pour 100 000 dans la population générale (25-74 ans) et par an. L’incidence augmentait avec l’âge et était plus élevée chez les hommes (157) que chez les femmes (127). Selon le Questionnaire sur l’Angine de Poitrine d’après Rose, la prévalence de l’angine de poitrine est de 2,6 % chez les hommes et de 3,1 % chez les femmes pour la population anglaise âgée de 16 ans et plus. Chez les personnes âgées de 75 ans et plus, 18 % des hommes et 17 % des femmes présentaient une angine de poitrine. L’évaluation de la douleur thoracique, en ville, par le médecin généraliste, sans investigation par un spécialiste, peut être difficile. Un nouveau modèle de soins, la Consultation d’Accès Rapide pour Douleur Thoracique, permet d’obtenir l’avis d’un spécialiste pour des patients de ville se présentant pour la première fois. Une telle consultation permet de poser le diagnostic, de stratifier le risque des patients présentant une angine de poitrine et d’orienter en priorité vers une investigation ultérieure par un spécialiste et, le cas échéant, vers une revascularisation. À plus long terme, les changements de mode de vie, les modifications des facteurs de risque et les traitements prophylactiques représentent un potentiel prometteur pour réduire le risque d’évolution vers l’infarctus du myocarde ou une issue fatale.
Clinical assessment of patients with stable angina
by L. Tavazzi, Italy

The clinical assessment of a patient with stable angina includes both a diagnostic process (at the onset of new symptoms) and a prognostic process. The diagnostic process is based on symptom evaluation, resting ECG, and echocardiography, as well as exercise ECG and imaging. The sensitivity of exercise ECG is modest (<50% when diagnostic workup bias is minimized), whereas specificity is relatively higher (around 85%). Exercise imaging has higher sensitivity, with echocardiography showing the highest discrimination. The prognostic process includes the same steps. Exercise imaging provides important information for prognostic stratification and subsequent decision-making, in particular when evaluating the presence and extent of viable myocardium. Outcome studies show that this is the main clinical issue. Although the various imaging techniques show no major differences in predicting prognostic benefit with revascularization, dramatic differences are noted in terms of survival according to the extent of viable myocardium and the therapeutic strategy employed. In the absence of myocardial viability, the reported mortality rate is similar whether patients are treated medically or surgically; in contrast, mortality is much lower in patients with myocardial viability undergoing revascularization, compared with medical treatment. Evidencing viable myocardium and evaluating its extent is therefore critical to risk stratification in patients with chronic ischemic heart disease.

Diagnosis

The diagnostic process begins with the evaluation of symptoms and signs. To characterize the chest pain, five criteria are considered: quality, location, duration of pain, triggering factors, and factors that relieve the pain. Based on these criteria, chest pain can be qualified as typical angina, atypical angina, or noncardiac chest pain. Typical angina is defined as substantial chest discomfort with a characteristic quality and duration, which is provoked by exertion or emotional stress and relieved by rest or nitroglycerin. Atypical angina meets two of the above criteria, and noncardiac chest pain meets one or none of the typical angina characteristics.

When there is sufficient suspicion of heart disease to warrant cardiac evaluation, the clinician should make a probability estimate of the likelihood of CAD. The likelihood of CAD varies strongly according to the extent of viable myocardium and the therapeutic strategy employed. In the absence of myocardial viability, the reported mortality rate is similar whether patients are treated medically or surgically; in contrast, mortality is much lower in patients with myocardial viability undergoing revascularization, compared with medical treatment. Evidencing viable myocardium and evaluating its extent is therefore critical to risk stratification in patients with chronic ischemic heart disease.
to (correct) characterization of symptoms, and the age and sex of the subject. In turn, this estimate markedly affects the diagnostic utility of the next step, the standard exercise test, the interpretation of which, in terms of posttest likelihood of CAD, can vary from 5% to 50% to 90% according to the pretest estimated likelihood.

Resting investigations can also be of help. The resting ECG is normal in about half of the patients with chronic stable angina. A normal resting ECG does not exclude severe CAD, but is associated with normal left ventricular function in about 95% of patients. Resting echocardiography is a useful tool for aiding the diagnosis of CAD, for a number of well-known reasons, such as analysis of regional ventricular contraction and mechanical ventricular function.

A meta-analysis of 147 published reports describing about 24,000 patients who underwent both coronary angiography and exercise testing reported a wide variation in sensitivity and specificity of exercise testing in the diagnosis of obstructive CAD. Mean sensitivity and specificity were 68% and 77%, respectively. When the analysis considered only results from the 58 studies that focused on diagnostic tests by excluding patients with prior MI, sensitivity was 67% and specificity 72%. When the analysis was restricted to the few studies that avoided diagnostic workup bias by including only patients who agreed before any testing to have both exercise testing and coronary angiography, sensitivity was 50% and specificity 90%. In a more recent study of 814 men that was carefully designed to minimize workup bias, sensitivity was 45% and specificity 85%. Therefore, the true diagnostic value of exercise ECG lies in its relatively high specificity. The sensitivity of exercise ECG is modest, generally lower than the sensitivity of imaging procedures.

With respect to pretest likelihood, posttest likelihood of CAD decreases if the ST segment does not shift significantly. If the ST segment shows a shift greater than 1 mm, diagnostic probability does not change much in patients with high pretest probability, but increases markedly in those with low pretest probability. The magnitude of ST-segment shifts is relevant in patients with low pretest probability, making the diagnosis almost certain for degrees of ST-segment depression greater than 2 mm. Diagnostic testing is most valuable when the pretest probability of obstructive CAD is intermediate. In published research, the arbitrary definition of intermediate probability is between 10% and 90% or within 20% and 80%.

Women and the elderly make up special groups of patients. Exercise testing is less sensitive in women than in men and some studies have found it to be also less specific. In a recent meta-analysis of 19 studies including 3721 women, sensitivity for diagnostic CAD was 61% and specificity 70%. However, according to the American College of Cardiology/American Heart Association (ACC/AHA) Guidelines, current data are insufficient to justify replacing standard exercise testing with stress imaging when evaluating women for CAD. In many women with a low pretest likelihood of disease, a negative exercise test result will be sufficient, and imaging procedures are not required. This is mainly explained by the fact that exercise testing has a high negative predictive power in women.

For a variety of reasons exercise testing in the elderly is more difficult to perform and to interpret. The greater severity of coronary disease in this group increases the sensitivity of exercise testing to about 85%, but also decreases specificity to about 70%. Despite these limitations, exercise testing remains important in the elderly, because they are a high-risk group.

The next step in the diagnostic process is stress imaging in those cases in which it can provide additional risk prediction information. This is the case in patients with typical anginal symptoms and normal or nondiagnostic exercise ECG, those with atypical angina or absence of symptoms with a positive exercise ECG, special subgroups of patients, such as those unable to exercise or with uninterpretable ECG or those with typical angina and a positive exercise ECG where false-positive stress tests are common (younger women). Stress imaging can be performed by using echocardiography or perfusion imaging. According to the ACC/AHA Guidelines, the advantages of echocardiography are: (i) higher specificity; (ii) versatility; more extensive evaluation of cardiac anatomy and function; (iii) greater convenience/efficacy/availability; and (iv) lower cost. The advantages of perfusion imaging are: (i) higher technical success rate; (ii) higher sensitivity, especially for one-vessel coronary disease; (iii) better accuracy in evaluating possible ischemia when multiple resting wall-motion abnormalities are present; and (iv) more extensive published databases, especially regarding evaluation of prognosis.

In a meta-analysis of 44 studies published between 1990 and 1997 comparing the diagnostic performance of exercise (Ex)-ECHO and Ex–single photon emission computed tomography (SPECT), Ex-ECHO had a sensitivity of 87% and a specificity of 77%, while Ex-SPECT yielded a similar sensitivity of 87%, but a lower specificity of 64%. Both Ex-ECHO and Ex-SPECT performed significantly better than Ex-ECG testing. Ex-ECHO was associated with significantly better discriminatory power than Ex-SPECT, even in subjects with known CAD.

An overview of the diagnostic performance of stress-imaging techniques for the detection of CAD showed a similar high sensitivity of both qualitative and quantitative perfusion techniques with a slightly higher sensitivity for tomographic than planar images in exercise testing, and a somewhat lower sensitivity for dipyridamole scintigraphy. Both exercise and dobutamine ECHO stress testing had a similar, slightly lower, sensitivity, but a significantly higher specificity. Two further meta-analyses were recently published. One, by a Dutch group, confirmed a slightly higher sensitivity, but a significantly lower specificity of nuclear imaging for the detection of CAD. Another meta-analysis, already mentioned, of the performance of imaging stress testing to detect CAD in women, showed that the perfusion scintigraphy technique slightly increased the low sensitivity of ECG without consistently
changing specificity. In this case, ECHO testing had the best sensitivity and an acceptable specificity (Table I). In women, thallium planar imaging was more specific than tomographic imaging.

The noninvasive assessment of a subject with suspected CAD should lead to the diagnosis of ischemic heart disease or to the exclusion of this diagnosis. Coronary angiography should be performed mainly for therapeutic purposes. Direct referral for diagnostic CAD may be indicated in patients with chest pain possibly attributable to myocardial ischemia when noninvasive testing is contraindicated or unlikely to be appropriate because of illness (for instance, heart failure), disability, or physical characteristics.1

Prognosis

As for diagnosis, prognostication in chronic ischemic heart disease is based on a cascade of incremental information: symptoms and signs, resting instrumental investigations, functional noninvasive assessment, and coronary angiography.

Several studies have examined the value of the characteristics of pain associated with other clinical information: symptoms and signs, resting instrumental investigations, functional noninvasive assessment, and coronary angiography.

The ESC guidelines provide a platform for prognostication. In general, the outcome is worse (and the revascularization-related improvement greater) in patients with worse left ventricular function, a greater number of diseased vessels, more proximal locations of coronary stenosis, greater severity of lesions, more severe angina, more easily provoked angina or ischemia, and greater age.

Resting ECG and ECHO can be of help for a variety of obvious reasons. A normal ECG is an indicator of good prognosis because, as already mentioned, it is associated with a normal left ventricular (LV) function in about 95% of cases.2 Resting echocardiography is a pivotal prognostic tool. Thus, the Coronary Artery Surgery Study (CASS) registry, as far back as 20 years ago, showed a 12-year survival rate of 73% in patients with a left ventricular ejection fraction (LVEF) ≥50% and 21% in patients with a LVEF <35%.3

Ex-ECG is the first recommended step in the prognostic stratification of patients who are not taking digoxin, have a normal resting ECG, and are able to exercise.4 The Duke treadmill score combines the most significant information provided by exercise testing: exercise performance, symptoms, and the electrophysiologic signs of induced myocardial ischemia (the ST-segment shift). In several studies, the score worked well for both inpatients and outpatients, and preliminary data suggest that the score works equally well for men and women.5,6 Several studies have highlighted both the diagnostic and the prognostic performance of further exercise test parameters: chronotropic incompetence, abnormal heart rate recovery, and delayed systolic blood pressure response. However, the recent update of the ACC/AHA Guidelines for exercise test...

**Table III. Exercise (Ex)-ECG or Exercise (Ex)-ECHO in clinical practice. Risk-adjusted rates of catheterization and revascularization.**

<table>
<thead>
<tr>
<th>Posttest risk:</th>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ex-ECHO</td>
<td>Ex-ECG</td>
<td>Ex-ECHO</td>
</tr>
<tr>
<td>Catheterization</td>
<td>7%</td>
<td>59%</td>
<td>17%</td>
</tr>
<tr>
<td>Revascularization</td>
<td>12%</td>
<td>35%</td>
<td>25%</td>
</tr>
</tbody>
</table>


**Table IV. Accuracy of different viability techniques to predict recovery after revascularization. A meta-analysis.**

<table>
<thead>
<tr>
<th>Technique</th>
<th>Studies (n)</th>
<th>Patients (n)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dob-ECHO</td>
<td>32</td>
<td>1090</td>
<td>81</td>
<td>80</td>
</tr>
<tr>
<td>TI-201 RR</td>
<td>22</td>
<td>557</td>
<td>86</td>
<td>59</td>
</tr>
<tr>
<td>TI-201 RI</td>
<td>11</td>
<td>301</td>
<td>88</td>
<td>50</td>
</tr>
<tr>
<td>MIBI</td>
<td>20</td>
<td>488</td>
<td>81</td>
<td>66</td>
</tr>
<tr>
<td>FDG-PET</td>
<td>20</td>
<td>598</td>
<td>93</td>
<td>58</td>
</tr>
</tbody>
</table>


An important clinical issue is the prognostic stratification leading to therapeutic decision-making in patients with LV dysfunction, in particular, the detection of viable myocardium. The most frequently used techniques are dobutamine stress ECHO and thallium reinjection or rest-redistribution. Two meta-analyses addressed this issue. One showed a relatively high sensitivity of the different techniques, but the specificity of the nuclear technique in predicting the recovery of asynergic myocardium after revascularization is much lower than that of dobutamine stress ECHO (Table IV). This difference in sensitivity and specificity between the two techniques was highlighted by pooling the data of 17 studies in which a head-to-head comparison between dobutamine stress ECHO and nuclear imaging was performed.

In another meta-analysis of 24 studies including over 3000 patients, the primary goal was not the comparison among different techniques in detecting viable myocardium, but the predictive power of the long-term outcome of patients undergoing myocardial viability testing. The mortality was not predicted differently by thallium-perfusion imaging, fluorodeoxyglucose metabolic imaging, or dobutamine stress ECHO. Specifically, there was no measurable difference between techniques in predicting prognostic benefit with revascularization. This might suggest that the small differences observed among the tested techniques in predicting recovery of myocardial regions after revascularization impact little on late survival. In contrast, major differences were noted on survival in relation to either the presence of viable myocardium or the therapeutic strategy. In patients without myocardial viability, the mortality rate was similar in patients treated medically or surgically. In contrast, the annual high risk by Ex-ECG. Surprisingly enough, 35% of patients classified as low risk by the Duke score were revascularized vs only 30% of those classified at high risk, whereas the percentages were 12% vs 41% in patients classified by the ECHO findings.

Overall, the main characteristics of Ex-ECHO as a prognostic tool in stable chronic angina can be summarized as follows: (i) it is sensitive and specific for detecting inducible myocardial ischemia; (ii) a negative test in patients with a positive ECG response predicts a low risk of events; (iii) presence of inducible ischemia is independent and incremental to clinical and exercise data in predicting cardiac events in both men and women; and (iv) both dobutamine and exercise stress ECHO have higher sensitivity than vasodilator stress ECHO tests.

Stress perfusion imaging is also largely used for prognostic purposes in stable angina patients. The main findings coming out from several studies can be summarized as follows: (i) normal poststress thallium scans are highly predictive of a benign prognosis; (ii) predictors of high risk are: number, size, and location of perfusion abnormalities, amount of thallium 201 lung uptake, poststress LV dilatation; and (iii) the combination of stress perfusion and stress ventricular function assessment does not increase the prognostic power with respect to each stress test taken singly.

A comparative summary of the characteristics of the different techniques used in patients with chronic CAD was also reported in the European Guidelines, which showed that Ex-ECG has a greater sensitivity in patients with multivessel disease, whereas thallium scintigraphy, which is based on comparative perfusion in different myocardial regions, is most sensitive in single-vessel disease. Echo stress can be sensitive in both cases. The sensitivity of thallium scintigraphy is lower when the inferior wall of the left ventricle is the target ventricular region.

**Myocardial viability**

An important clinical issue is the prognostic stratification leading to therapeutic decision-making in patients with LV dysfunction, in particular, the detection of viable myocardium. The most frequently used techniques are dobutamine stress ECHO and thallium reinjection or rest-redistribution. Two meta-analyses addressed this issue. One showed a relatively high sensitivity of the different techniques, but the specificity of the nuclear technique in predicting the recovery of asynergic myocardium after revascularization is much lower than that of dobutamine stress ECHO (Table IV). This difference in sensitivity and specificity between the two techniques was highlighted by pooling the data of 17 studies in which a head-to-head comparison between dobutamine stress ECHO and nuclear imaging was performed.

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death rate was about 80% lower in patients with myocardial viability in whom revascularization was performed, with respect to those treated medically (mortality rate 3% vs 16%).

These findings pose a further question: should all patients with abnormal left ventricular kinetics and function undergo a viability test in order to define the most appropriate therapeutic strategy or should they be directed straight to coronary angiography? To answer this question, a prospective multicenter observational study, the Economics of Noninvasive Diagnosis (END) study, was performed, which enrolled 11,372 patients and followed them up for an average of 2.5±1.5 years.23 The study showed a similar outcome whether patients underwent an aggressive strategy consisting in direct cardiac catheterization or a conservative strategy with initial stress myocardial perfusion tomography followed by coronary angiography when indicated. However, the revascularization rate was twice as high in the direct cardiac catheterization strategy. Interestingly, the revascularization rate was higher in all clinical risk classes. Thus, once the coronary angiography was performed, the decision to proceed with revascularization was independent of the patients’ risk grading. Consequently, the cost per patient was higher in the aggressive strategy, and as the outcome was similar, cost-effectiveness was lower. Similar results were obtained in the Economics of Myocardial Perfusion Imaging in Europe (EMPIRE) study, which compared the cost-effectiveness of four diagnostic strategies including or not myocardial perfusion imaging.24 The 2-year patient outcome was the same, irrespective of strategy, but the use of imaging was associated with lower total cost because of the performance of less angiography and revascularization. In conclusion, it appears that the decision to revascularize is strictly linked to the process of risk assessment, and the performance of coronary angiography does not necessarily translate into a different outcome.

Based on these findings, the ACC/AHA Guidelines1 recommend invasive strategy only if the patient’s prognosis on medical therapy is poor and can be improved by revascularization. Coronary angiography is considered inappropriate when the estimated annual mortality rate is ≤1% (low risk with noninvasive risk stratification). The same guidelines classify the low-risk patients as those with a low-risk treadmill score (>5), normal or small myocardial perfusion defect at rest or with stress, and normal stress echocardiographic wall motion or no change of limited resting wall motion abnormalities during stress. This does not reflect the current practice in hospitals with catheterization and coronary intervention facilities.

The indications for performing coronary angiography according to the European Guidelines are: (i) severe angina (class 3 CCS); (ii) class I-II angina if there is a history of MI or myocardial ischemia at low workload; (iii) bundle branch block with inducible myocardial ischemia; (iv) revascularized patients with recurrent angina; and (v) severe ventricular asynergy and when essential for clinical or occupational reasons.

The decision on which strategy to use, medical or interventional, is also based on the prognostic relevance of the anatomy of the coronary artery, as summarized in Table V. The 5-year survival rate is largely dependent on the extent and severity of the obstruction of the coronary vessels. Longer-term observations from the CASS registry also confirm the prognostic significance of the rough classification of CAD in 1-, 2-, or 3-vessel disease.25 This obviously supports the interventional therapeutic approach. However, we know that most events in patients with ischemic heart disease are induced by the destabilization of angiographically irrelevant nonobstructive coronary lesions. In spite of that, from the prognostic point of view, the severity of the obstructive coronary disease is important probably because there is a correlation between the severity and diffusion of the obstructive lesions and the aggressiveness of the atherosclerotic disease.

Patients with stable angina after revascularization represent a special and growing group of patients. Post–percutaneous coronary intervention (PCI) restenosis and vein graft stenosis commonly induce silent ischemia. Moreover, saphenous vein graft lesions represent a rather unstable form of atherosclerosis prone to rapid progression and thrombotic complications.26,27 Ex-ECG is an insensitive predictor of such events, with a sensitivity ranging from 40% to 55%, significantly less than with Ex-SPECT28 or Ex-ECHO.29 Because of these considerations and the need to document the site of ischemia, stress imaging tests are preferred for evaluating patients belonging in this group. Obviously, the rationale of this approach is that ischemia, whether painful or silent, worsens the prognosis. However, the prognostic benefit of controlling silent ischemia still needs to be proven. Some new findings seem to support this concept. For instance, an observational study on 307 patients undergoing stress myocardial perfusion testing after PCI showed a much higher event rate (death and MI) in patients with inducible myocardial ischemia than in those without ischemia.29 Further data are scheduled to be soon published in the literature and should shed more light on this crucial issue.

<table>
<thead>
<tr>
<th>Extent of CAD (0-100) (%)</th>
<th>Prognostic weight</th>
<th>5-year survival rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-vessel disease, 75%-95%</td>
<td>23-32</td>
<td>91-93</td>
</tr>
<tr>
<td>&gt;1 vessel disease, 50% to 74%</td>
<td>23-32</td>
<td>93</td>
</tr>
<tr>
<td>2-vessel disease</td>
<td>37</td>
<td>88</td>
</tr>
<tr>
<td>2-vessel disease, both ≥ 95%</td>
<td>42-86</td>
<td>79</td>
</tr>
<tr>
<td>2-vessel disease, both ≥ 95% proximal LAD</td>
<td>56-79</td>
<td>79</td>
</tr>
<tr>
<td>3-vessel disease</td>
<td>56-79</td>
<td></td>
</tr>
<tr>
<td>3-vessel disease ≥ 95% in at least 1</td>
<td>63-73</td>
<td>73</td>
</tr>
<tr>
<td>3-vessel disease, 75%-95% proximal LAD</td>
<td>67-74</td>
<td>59-67</td>
</tr>
</tbody>
</table>

Table V. Risk stratification assuming medical treatment only.

Abbreviations: CAD, coronary artery disease; LAD, left anterior descending (coronary artery).

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tients with chronic stable angina. A report of the American Col-
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 outcome of patients with silent versus symptomatic ischemia six
months after percutaneous coronary intervention and stenting.

ÉVALUATION CLINIQUE DES MALADES ATTEINTS D’ANGOR STABLE

L’évaluation clinique d’un malade atteint d’angor stable inclut non seule-
ment un volant d’investigations diagnostiques, face à l’installation de
symptômes nouveaux, mais également un diagnostic pronostique. Le bilan
diagnostique repose sur l’évaluation des symptômes, l’analyse des données élec-
trocardiographiques et échocardiographiques au repos ainsi que sur l’ECG et
l’imagerie d’effort. La sensibilité de l’ECG d’effort est limitée (<50 %), même
quand les biais diagnostiques sont réduits au minimum, alors que sa spécifi-
cité est plus élevée (environ 85 %). L’imagerie d’effort, quant à elle, possède une
sensibilité plus élevée, le meilleur pouvoir de discrimination revenant aux
techniques échocardiographiques. L’évaluation pronostique fait appel aux mêmes
métodes d’investigation. Les tests d’effort fournissent des données importantes
pour la stratification pronostique et la prise de décision, en particulier en ce qui
concerne l’estimation de la viabilité myocardique et de son étendue. Les études
d’issues montrent qu’il s’agit là du problème clinique principal. Les diverses
techniques d’imagerie ne montrent guère de différences en termes de prédiction
des bénéfices pronostiques de la revascularisation myocardique. En revanche,
des différences de survie conséquentes sont notées en fonction de la présence
de myocarde viable et des stratégies thérapeutiques utilisées. En l’absence de
viabilité myocardique, les taux de mortalité sont similaires, que le traitement
soit médical ou chirurgical. À l’opposé, en présence d’un myocarde viable, ces
taux sont nettement inférieurs en cas de revascularisation chirurgicale com-
parativement aux stratégies médicales. Ainsi, la mise en évidence d’un myo-
carde viable et l’évaluation de son étendue constituent une composante essen-
tielle pour la stratification du risque au cours des cardiopathies ischémiques
chroniques.
Interventional treatments in patients with stable angina

by A. T. L. Ong and P. W. Serruys, The Netherlands

Ischemic heart disease is a major global public health problem. In the United States alone, it accounts for 1 in 4.8 deaths. Chronic stable angina is the initial manifestation in approximately half of the cases and is estimated to afflict 16 500 000 Americans. It is a condition for which interventional treatment often results in good symptom relief. Furthermore, revascularization improves mortality in patients with significant left coronary artery disease, and in patients with three-vessel disease with left ventricular impairment. The use of balloon angioplasty confirmed the superiority of revascularization compared with medical therapy for symptom relief. It has since been superseded by the proen superiority of bare metal stenting, and, following the results of recent trials, is being replaced by drug-eluting stents. Coronary artery bypass surgery confers no survival advantage over stenting for multivessel disease, the main limitation of stenting being an increased need for reintervention due to restenosis. With the advent of drug-eluting stents, this limitation may soon disappear. Irrespective of the mode of intervention, risk factor modification, such as smoking cessation, strict glycemic and blood pressure control, and aggressive pharmacotherapy with antiplatelet agents, statins, angiotensin-converting enzyme (ACE) inhibitors, and β-blockers are vital to preserve the revascularization procedure and reduce future events. New studies such as SYNTAX (SYnergy between percutaneous coronary intervention with TAXus and cardiac surgery) and FREEDOM (Future Revascularization Evaluation in patients with Diabetes mellitus: Optimal management of Multivessel disease) are planned to address the contemporary role of drug-eluting stenting compared with coronary artery bypass surgery.


Keywords: stable angina; coronary artery bypass surgery; percutaneous coronary intervention; drug-eluting stent; statin; ACE inhibitor

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Interventional options

Interventional options are divided into CABG and PCIs. CABG was initially performed with saphenous vein grafts, but today involves the use of the left internal mammary artery and, in some cases, total arterial grafting with use of the right internal mammary artery and gastroepiploic artery. PCIs began with balloon angioplasty in 1977, and following landmark trials with coronary stenting (BENESTENT [BElgian-NETHERlands STENT], STRESS [STent RESTenosis Study]3), over 90% of PCIs performed today involve stent implantation. A large arsenal of adjunctive devices are available and may be utilized to facilitate stent implantation and in-


<table>
<thead>
<tr>
<th><strong>Trial acronyms</strong></th>
<th><strong>Description</strong></th>
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<tbody>
<tr>
<td>ACIP</td>
<td>Asymptomatic Cardiac Ischemia Pilot</td>
</tr>
<tr>
<td>ACME</td>
<td>Angioplasty Compared to MEdicine</td>
</tr>
<tr>
<td>ARTS</td>
<td>Arterial Revascularization Therapy Study</td>
</tr>
<tr>
<td>AWESOME</td>
<td>Angina With Extremely Serious Operative Mortality Evaluation</td>
</tr>
<tr>
<td>BENESTENT</td>
<td>BElgian-Netherlands STENT</td>
</tr>
<tr>
<td>CASS</td>
<td>Coronary Artery Surgery Study</td>
</tr>
<tr>
<td>ECSS</td>
<td>European Coronary Surgery Study</td>
</tr>
<tr>
<td>ERACII</td>
<td>Argentine Randomized Study: Coronary Angioplasty with Stenting vs Coronary Bypass Surgery in Multivessel Disease</td>
</tr>
<tr>
<td>EUROPA</td>
<td>European trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease</td>
</tr>
<tr>
<td>FIM</td>
<td>First-In-Man</td>
</tr>
<tr>
<td>FREEDOM</td>
<td>Future Revascularization Evaluation in patients with Diabetes mellitus: Optimal management of Multivessel disease</td>
</tr>
<tr>
<td>HOPE</td>
<td>Heart Outcomes Prevention Evaluation</td>
</tr>
<tr>
<td>LIPS</td>
<td>Lescol Intervention Prevention Study</td>
</tr>
<tr>
<td>MASS</td>
<td>Medical, Angioplasty or Surgery Study</td>
</tr>
<tr>
<td>Post CABG</td>
<td>Post Coronary Artery Bypass Graft</td>
</tr>
<tr>
<td>RAPEL</td>
<td>Randomized study with the sirolimus-eluting VElocity balloon-expandable stent in the treatment of patients with de novo native coronary artery Lesions</td>
</tr>
<tr>
<td>RESEARCH</td>
<td>Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital</td>
</tr>
<tr>
<td>REVERSAL</td>
<td>Reversal of Atherosclerosis with Aggressive Lipid lowering</td>
</tr>
<tr>
<td>RITA</td>
<td>Randomized Intervention Trial for Angina</td>
</tr>
<tr>
<td>SIRIUS</td>
<td>acronym for sirolimus (SIRolImUS)</td>
</tr>
<tr>
<td>SOLVD</td>
<td>Studies Of Left Ventricular Dysfunction</td>
</tr>
<tr>
<td>SoS</td>
<td>Surgery or Stent</td>
</tr>
<tr>
<td>STRESS</td>
<td>Stent RSEstenosis Study</td>
</tr>
<tr>
<td>SYNTAX</td>
<td>SYnergy between percutaneous coronary intervention with TAXus and cardiac surgery</td>
</tr>
<tr>
<td>TAXUS</td>
<td>a trademark for paclitaxel-eluting coronary stents</td>
</tr>
<tr>
<td>VA</td>
<td>Veterans Administration (cooperative study)</td>
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</table>

- **Indication for intervention in stable angina**

Based on the trials that will be discussed below, revascularization is indicated in patients who have: (i) significant left main coronary artery disease; (ii) three-vessel disease, especially with abnormal left ventricular function; (iii) two-vessel disease with proximal left anterior descending (LAD) coronary artery involvement; (iv) one- or two-vessel disease with a large area of viable myocardium at risk; and (v) for the relief of symptoms. For patients who are not candidates for PCI or CABG, alternative therapies available include percutaneous or surgical laser transmyocardial revascularization, enhanced external counterpulsation, or spinal cord stimulation.³

- **Surgical revascularization versus medical therapy** (Table I)

The first landmark trial was the Veterans Administration (VA) cooperative study of 686 patients randomly assigned to surgery (n=332) or medical (n=354) treatment for chronic stable angina. In a subgroup of 91 patients with significant left main coronary artery disease, CABG was superior to medical therapy at 42 months.⁷ Excluding left main coronary artery lesions, there was no significant difference in mortality at 36 months, with 87% of the medical group and 88% of the surgical group alive. The randomized European Coronary Surgery Study (ECSS) of 768 patients demonstrated a significant survival benefit of surgery over medical therapy for its total population, in patients with three-vessel disease, and in patients with stenosis in the proximal third of the LAD coronary artery constituting a component of either two- or three-vessel disease.⁶ Patients with left main coronary artery disease showed a trend to benefit with surgery. In terms of angina and exercise performance, the surgical group did significantly better than the medical group throughout the 5 years of follow-up.

In the Coronary Artery Surgery Study (CASS) of 780 patients, no mortality differences were observed at 5- or 10-year follow-up between the CABG or medically treated groups.⁷ CABG, however, improved the quality of life as manifested by relief of chest pain, improvement in both subjective and objective measurements of functional status, and diminished requirement for drug therapy.¹⁰

- **PCI versus medical therapy** (Table I)

The Angioplasty Compared to MEdicine (ACME) study, published in 1992, was the first study to compare PCI with balloon angioplasty versus medical therapy.¹¹ A total of 212 patients with stable angina, positive exercise stress test, and significant stenosis of one artery were randomized to balloon angioplasty or medical therapy. At 6 months, more patients in the PCI group were angina-free compared with the medically treated group (64% versus 46%, P<0.01). Mortality and myocardial infarction were not different between the two groups.

The Randomized Intervention Trial for Angina (RITA)-2 randomized 1018 patients with 1-3 vessel disease to either PCI or medical treatment.¹² Stent use was only 9% in this study. At 2.7 years follow-up, there was no difference in mortality between the study groups. Early intervention with PCI was associated with greater symptomatic improvement and exercise tolerance, especially in patients with more severe angina.

The Asymptomatic Cardiac Ischemia Pilot (ACIP) study randomized 558 patients who had coronary anatomy suitable for revascularization to three treatment strategies: angina-guided drug therapy (n=183), angina plus ischemia-guided drug therapy (n=183), or revascularization by angioplasty or bypass surgery (n=192).¹³ Two years after randomization, total mortality was 6.6% in the angina-guided strategy, 4.4% in the ischemia-guided strategy, and 1.1% in the revascularization strategy (P<0.02). The rate of death or myocardial infarction...
was 12.1% in the angina-guided strategy, 8.8% in the ischemia-guided strategy, and 4.7% in the revascularization strategy (P<0.04). The rate of death, myocardial infarction, or recurrent cardiac hospitalization was 41.8% in the angina-guided strategy, 38.5% in the ischemia-guided strategy, and 23.1% in the revascularization strategy (P<0.001). Its importance is that this study is the only study to date to demonstrate a superiority of percutaneous revascularization over medical therapy regarding the end points of both mortality and death or myocardial infarction.

The Medical, Angioplasty or Surgery Study (MASS)\textsuperscript{14} was the first randomized trial to compare the three treatment strategies. It was a single-center study of 214 patients with single-vessel coronary artery disease involving the proximal LAD coronary artery with single operators in each group. Bypass surgery for single-vessel coronary artery disease is associated with a lower incidence of midterm and long-term events as well as fewer anginal symptoms than that found in the patients who underwent angioplasty or medical therapy. In this study, coronary angioplasty was only superior to medical strategies in relation to the anginal status. However, the three treatment regimens yielded a similar incidence of acute myocardial infarction and death.

\textbf{\textcolor{red}{M}}\textbf{PCI: stenting versus PTCA (Table II)}

At the same time, the development of coronary stents meant that a second avenue in PCI had opened. In patients who received a stent than in those who received standard coronary angioplasty. However, this benefit was achieved at the cost of a significantly higher risk of vascular complications at the access site and a longer hospital stay. At 1 year, no significant differences in mortality (1.2% vs 0.8%), stroke (0.0% vs 0.8%), myocardial infarction (5.0% vs 4.2%), or coronary bypass graft surgery (6.9% vs 5.1%) were found between the stent and balloon angioplasty groups, respectively. However, the requirement for a repeat angioplasty procedure was significantly lower in the stent group (10%) than the balloon angioplasty group (21%, \textit{P}<0.001).\textsuperscript{15}

In the United States, STRESS\textsuperscript{5} mirrored the findings of BENESTENT. A total of 410 patients were randomized to elective stent placement or balloon angioplasty. Stent placement resulted in an improved rate of procedural success, a lower rate of angiographically detected restenosis, a similar rate of clinical events after 6 months, and a less frequent need for revascularization of the original coronary lesion.

\textbf{\textcolor{red}{M}}\textbf{PCI: stenting versus CABG (Table II)}

The four most contemporary studies comparing

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\begin{table}
\centering
\begin{tabular}{|l|c|c|c|c|c|c|c|}
\hline
\textbf{Trial} & \textbf{Years enrolled} & \textbf{Vessels treated} & \textbf{Follow-up (years)} & \textbf{Treatment} & \textbf{Patients (n)} & \textbf{Mortality (%)} & \textbf{Death or MI (%)} & \textbf{Freedom from angina (%)} \\
\hline
\textbf{CABG vs medical therapy} & & & & & & & & \\
\textit{VA} & 1972-4 & \geq 1 & 3 & CABG & 310 & 12 & - & - \\
& & & & Medical & 286 & 13 & - & - \\
\textit{VA} & 1972-4 & Left main & 3.5 & CABG & 48 & 12* & - & - \\
& & & & Medical & 43 & 35* & - & - \\
\textit{ECSS} & 1973-6 & \geq 1 & 5 & CABG & 394 & 8* & - & 46* \\
& & & & Medical & 373 & 15* & - & 28* \\
\textit{CASS}\textsuperscript{5,10} & 1975-9 & \geq 1 & 5 & CABG & 390 & 3 & - & 60*\textsuperscript{†} \\
& & & & Medical & 390 & 3 & - & 35*\textsuperscript{†} \\
\hline
\textbf{PCI-balloon vs medical therapy} & & & & & & & & \\
\textit{ACME}\textsuperscript{11} & 1987-90 & 1 & 0.5 & PCI & 105 & 0 & 4.8 & 64* \\
& & & & Medical & 107 & 0.9 & 3.7 & 46* \\
\textit{RITA-2}\textsuperscript{12} & 1992-6 & \geq 1 & 2.7 (median) & PCI & 504 & 2.2 & 6.3* & 70*\textsuperscript{†} \\
& & & & Medical & 514 & 1.4 & 3.3* & 50*\textsuperscript{†} \\
\hline
\textbf{Intervention vs medical therapy} & & & & & & & & \\
\textit{ACIP}\textsuperscript{13} & 1991-3 & \geq 1 & 2 & PCI/CABG & 183 & 6.6* & 12.1* & - \\
& & & & Angina-guided medical & 183 & 4.4* & 8.8* & - \\
& & & & Angina + ischemia-guided medical & 192 & 1.1 & 4.7 & - \\
\textit{MASS}\textsuperscript{14} & 1988-91 & Proximal LAD & 3 (mean) & PCI & 72 & 1.4 & - & 82* \\
& & & & CABG & 70 & 2.9 & - & 98* \\
& & & & Medical & 72 & 0 & - & 34* \\
\hline
\end{tabular}
\caption{Randomized trials of intervention versus medical therapy for stable angina.}
\end{table}
PCI and surgery involve the use of coronary stenting. The Arterial Revascularization Therapy Study (ARTS),16 Surgery or Stent (SoS) trial,17 Argentinian Randomized Study: Coronary Angioplasty With Stenting Versus Coronary Bypass Surgery in Patients With Multiple-Vessel Disease (ERACI II),18 and Angina With Extremely Serious Operative Mortality Evaluation (AWESOME) trial19 enrolled patients between 1995 and 2000. ERACI II and AWESOME were predominantly unstable angina studies.

The ARTS trial randomized 1205 patients in 69 centers to either stenting (n=600) or coronary artery bypass surgery (n=605) for the treatment of multivessel disease. At 1 and 3 years, there were no differences in mortality, myocardial infarction or CVA between the groups.20,21 The primary end point was a composite of freedom from death, myocardial infarction (MI), cerebrovascular accident (CVA), and any repeat revascularization at 1 year, and was lower in the stent group (73.8% versus 87.8%, P<0.001), driven by an increased need for repeat revascularization in the stent group (21.0% versus 3.8%, P<0.001). By 3 years, the incidence of repeat revascularization was 26.7% versus 6.6%, respectively (P<0.001). Stenting was, however, more cost-effective by €2779 at the end of 1 year compared with surgery. At 3 years this was reduced to €1798.

The SoS trial randomized 988 patients in 53 centers with symptomatic multivessel disease to either stent-assisted PCI (n=488) or CABG (n=500) and reported its results with a median follow-up of 2 years. The primary outcome of repeat revascularization was significantly higher in the PCI group (21% versus 6%, P<0.0001).

Table II. Randomized trials of stenting versus balloon angioplasty or bypass surgery.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Years enrolled</th>
<th>Vessels treated</th>
<th>Follow-up (years)</th>
<th>Treatment</th>
<th>Patients (n)</th>
<th>Mortality (%)</th>
<th>Repeat revascularization (%)</th>
<th>Angiographic restenosis (%)</th>
<th>Freedom from angina (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCI-stent versus PCI-balloon</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BENESTENT1</td>
<td>1996-3</td>
<td>1</td>
<td>0.7</td>
<td>Stent</td>
<td>262</td>
<td>0.8</td>
<td>10.0*</td>
<td>22*</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Balloon</td>
<td>258</td>
<td>0.4</td>
<td>20.6*</td>
<td>32*</td>
<td>66</td>
</tr>
<tr>
<td>STRESS3</td>
<td>1991-3</td>
<td>1</td>
<td>0.7</td>
<td>Stent</td>
<td>207</td>
<td>1.5</td>
<td>11.2</td>
<td>32*</td>
<td>79</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Balloon</td>
<td>203</td>
<td>1.5</td>
<td>12.4</td>
<td>42*</td>
<td>71</td>
</tr>
<tr>
<td>PCI-stent versus CABG</td>
<td></td>
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<td></td>
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<td></td>
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<tr>
<td>SoS22</td>
<td>1996-9</td>
<td>≥2</td>
<td>2.7 (median)</td>
<td>Stent</td>
<td>471</td>
<td>4.5*</td>
<td>20.7*</td>
<td>-</td>
<td>66*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CABG</td>
<td>493</td>
<td>1.6*</td>
<td>6.0*</td>
<td>-</td>
<td>79*</td>
</tr>
<tr>
<td>ARTS-1 year20</td>
<td>1997-8</td>
<td>≥2</td>
<td>1</td>
<td>Stent</td>
<td>600</td>
<td>2.5</td>
<td>21.0*</td>
<td>-</td>
<td>79*</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CABG</td>
<td>605</td>
<td>2.8</td>
<td>3.8*</td>
<td>-</td>
<td>89*</td>
</tr>
<tr>
<td>ARTS-3 year21</td>
<td>1997-8</td>
<td>≥2</td>
<td>3</td>
<td>Stent</td>
<td>600</td>
<td>3.7</td>
<td>26.7*</td>
<td>-</td>
<td>72*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CABG</td>
<td>605</td>
<td>4.6</td>
<td>6.6*</td>
<td>-</td>
<td>87*</td>
</tr>
</tbody>
</table>

*P<0.05.

PCI and surgery involve the use of coronary stenting. The Arterial Revascularization Therapy Study (ARTS),16 Surgery or Stent (SoS) trial,17 Argentinian Randomized Study: Coronary Angioplasty With Stenting Versus Coronary Bypass Surgery in Patients With Multiple-Vessel Disease (ERACI II),18 and Angina With Extremely Serious Operative Mortality Evaluation (AWESOME) trial19 enrolled patients between 1995 and 2000. ERACI II and AWESOME were predominantly unstable angina studies.

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PCI: drug-eluting stents (Table III)

The advent of drug-eluting stents began with the First-In-Man (FIM) study, utilizing a sirolimus-eluting stent.22 This was followed by the RAVEL (Randomized study with the sirolimus-eluting VElocity balloon-expandable stent in the treatment of patients with de novo native coronary artery Lesions),23 SIRIUS (SIRolImUS),24 E-SIRIUS,25 and C-SIRIUS26 randomized trials, which confirmed its superiority over bare metal stents. Similar results were obtained with a polymer-coated paclitaxel-eluting stent (tradename, TAXUS28), with the TAXUS-I, TAXUS-II,29 and TAXUS-IV29 randomized trials. These trials involved the use of a drug-eluting stent to treat a single coronary lesion. The first registry to publish extensively on the use of drug-eluting stents in a “real-world” setting with different subgroups was the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry.30 In a report of 99 consecutive
randomized to stenting were subdivided into two groups—complete (n=406) or incomplete (n=170) revascularization based on the diagnostic and procedural angiograms obtained at the core laboratory. At 1 year, freedom from major adverse cardiac and cerebrovascular events (MACCE) was higher in the group that was successfully completely revascularized (76.6% versus 69.4%, P<0.05).

Pharmacotherapy and risk factor modification following interventional treatment

**Statins**
Lipid lowering with statins has been conclusively shown to reduce events both as primary and as secondary prevention strategies, initially in hypercholesterolemic patients and later in patients with normal cholesterol levels.

The Lescol Intervention Prevention Study (LIPS) was the first randomized trial specifically designed to investigate whether cholesterol lowering with fluvastatin, initiated within days following successful completion of first PCI (with or without stenting) would prolong cardiac disease-free survival compared with placebo in patients with average (3.5-7.0 mmol/L) baseline cholesterol levels.34 This multicenter trial enrolled 1677 patients with stable angina or silent ischemia, median time to initiation of therapy was 2 days following PCI, and patients were followed-up for a median of 3.9 years. Stents were implanted in 56% of lesions (enrollment period April 1996 to October 1998). The primary outcome of MACE, defined as a composite of death, nonfatal myocardial infarction or reintervention demonstrated that the fluvastatin treated group enjoyed higher MACE-free survival (78.6% versus 73.3%, P<0.01).

In a substudy of LIPS, the investigators looked at patients who were exclusively treated with stenting (n=847, 50.5% of total cohort, fluvastatin [n= 417], placebo [n = 430]).35 During 4 years of follow-up, fluvastatin treatment decreased the risk of first adverse cardiac atherosclerotic events by 30% compared with placebo (P=0.03). When the data on revascularization were split into target and nontarget lesion revascularization, a significantly lower incidence of nontarget vessel revascularization was observed in the fluvastatin group (relative risk 0.47, 95% confidence interval 0.26 to 0.86, P=0.01). No difference was observed in target lesion revascularization between the two groups.

The recently published randomized, multicenter Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial looked at the value of aggressive lipid-lowering therapy with 80 mg of
Atorvastatin compared with 40 mg pravastatin and by intravascular ultrasound (IVUS) analysis and showed that for patients with coronary heart disease, intensive lipid-lowering treatment with atorvastatin reduced progression of coronary atherosclerosis compared with pravastatin.3,6,7 Compared with baseline values, patients treated with atorvastatin had no change in atheroma burden, whereas patients treated with pravastatin showed progression of coronary atherosclerosis.

Within the surgical cohort, the Post Coronary Artery Bypass Graft (Post CABG) Trial, a multicenter randomized trial reported that aggressive lowering of low-density lipoprotein (LDL) cholesterol levels to below 100 mg/dL reduced the progression of atherosclerosis in patients who had at least two patent saphenous vein grafts. Patients were followed-up for a mean of 4.3 years.27

**Angiotensin-converting enzyme inhibitors**

The cardiovascular protective effects of angiotensin-converting enzyme (ACE) inhibitors in patients with chronic stable angina has been well documented in all subgroups of patients. Initial studies demonstrated a mortality benefit in patients with severe left ventricular dysfunction (Survival And Ventricular Enlargement [SAVE]38 and Studies Of Left Ventricular Dysfunction [SOLVD]39). The Heart Outcomes Prevention Evaluation (HOPE) trial confirmed that the use of ramipril 10 mg per day reduced cardiovascular death, MI, or stroke (either a composite or each individual component) in patients who were at high risk, or had vascular disease in the absence of heart failure.40

More recently, the European trial on Reduction Of cardiac events with Perindopril in patients with stable coronary Artery disease (EUROPA) study randomized 12,218 patients to perindopril or placebo with a mean follow-up of 4.2 years.41 Perindopril treatment was associated with a significant reduction in the primary end point (cardiovascular mortality, nonfatal myocardial infarction, and resuscitated cardiac arrests, P=0.0003) in a broad population of patients with stable coronary artery disease and no evidence of overt heart failure (20% relative risk reduction and 1.9% absolute risk reduction). Cardiovascular death, myocardial infarction, cardiac arrest, acute coronary syndromes, and development of heart failure were all reduced. The benefit began to appear at 1 year and gradually and progressively increased throughout the duration of the trial.

**β-Blockers**

β-Blocker use has been shown to be useful in the management of hypertension, angina, in the post-myocardial infarction setting and in patients with left ventricular dysfunction.7 Patients with chronic stable angina post intervention may fulfill any of the above criteria and are candidates for therapy.

**Antiplatelet agents**

Aspirin (75 to 325 mg daily) is recommended routinely in all patients with acute and chronic ischemic heart disease irrespective of symptoms.8 It has also been shown to improve patency of vein grafts following bypass surgery.

**Diabetes**

Diabetes is associated with a poor outcome in patients with established coronary artery disease, even after angiographic and other clinical characteristics are considered. The incidence of restenosis is consistently higher in diabetic compared with nondiabetic patients, even in the era of drug-eluting stents.24,29 Current recommendations prescribe strict glycemic control in diabetic patients with chronic stable angina with the belief that this will provide benefits with regard to microvascular complications and also may reduce risk for other cardiovascular disease complications despite a paucity of data.2

**Smoking**

Clinical data to date strongly suggest that smoking cessation reduces the risk of cardiovascular events.2 Although no randomized clinical trials of smoking cessation have been performed in patients with chronic stable angina, three such trials have been performed in a primary prevention setting and smoking cessation was associated with a reduction of 7% to 47% in cardiac event rates.

**Conclusion**

Chronic stable angina is a condition for which interventional treatment often results in good symptom relief. Revascularization improves mortality in patients with significant left main coronary artery disease, and in patients with three-vessel disease with left ventricular impairment. The use of balloon angioplasty confirmed the superiority of revascularization compared with medical therapy for symptomatic relief. It has since been superseded by the proven superiority of bare metal stenting, and following the results of recent trials, is being replaced by drug-eluting stents. CABG confers no survival advantage over stenting for multivessel disease, the main limitation of stenting being an increased need for reintervention due to restenosis. With the advent of drug-eluting stents, this limitation may soon disappear. Irrespective of the mode of intervention, risk factor modification, such as smoking cessation, strict glycemic and blood pressure control, and aggressive pharmacotherapy with antiplatelet agents, statins, ACE inhibitors, and β-blockers are vital to preserve the revascularization procedure and reduce future events. New studies such as SYNTAX and FREEDOM are planned to address the contemporary role of drug-eluting stenting compared to coronary artery bypass surgery. □
REFERENCES


Les traitements interventionnels au cours de l’angor stable

Les cardiopathies ischémiques chroniques constituent globalement un problème majeur en santé publique. Aux États-Unis, un décès sur 4,8 leur est imputable. L’angor chronique stable est la manifestation initiale de ces cardiopathies dans environ la moitié des cas. Ce symptôme qui affecterait 16 500 000 Américains constitue une condition dans laquelle les traitements interventionnels aboutissent souvent à de bons résultats symptomatiques. En outre, la revascularisation diminue la mortalité quand il existe une sténose du tronc commun de la coronaire gauche ou encore des lésions tritronculaires sténosantes associées à une altération de la fonction ventriculaire gauche. Le recours à l’angioplastie par ballonnet a confirmé la supériorité de la revascularisation sur le traitement médical pour ce qui est de l’effet symptomatique. Depuis, cette technique a été supplantée par la mise en place des stents métalliques nus qui ont fait la preuve de leur supériorité. À la lueur des résultats des études les plus récentes, ceux-ci tendent à être remplacés par les stents à élu-
tion de médicaments. Le pontage aorto-coronaire n’apporte pas d’avantage en termes de survie par rapport aux stents en cas d’atteinte pluritronculaire, la principale limitation de ceux-ci étant liée à la nécessité plus fréquente d’une ré-intervention du fait de la survenue d’une resténose. Avec l’avènement des stents à élu-
tion médicamenteuse, cette limite pourrait rapidement disparaître. Indé-
anon du mode d’intervention, la préservation des procédures de revas-
cularisation et la prévention des complications ultérieures passent par la cor-
rection des facteurs de risque, notamment l’arrêt du tabagisme, le contrôle strict de la glycémie et de la pression artérielle, ainsi que par le recours à une phar-
macothérapie agressive reposant sur les agents antiplaquettaires, les statines, les inhibiteurs de l’enzyme de conversion et les bétabloquants. Des études nou-
velles, telles SYNTAX (SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery) et FREEDOM (Future Resvascularization Evaluation in patiEnts with Diabetes mellitus: Optimal management of Multi-
tivesel disease), sont programmées pour évaluer le rôle des stents à élu-
tion de médicament, comparativement à la revascularisation par pontage aorto-
coronaire.
The goals of the treatment of angina pectoris/stable angina are to improve prognosis (ie, prolong life expectancy) by preventing death and/or myocardial infarction (MI) and to improve quality of life by treating and preventing the symptoms related to ischemia. Some of the therapies designed to relieve myocardial ischemia may be expected to impact on the risk of death and MI. Before reviewing the available therapies and discussing unmet needs, this paper first takes a look at the epidemiology of angina pectoris.

**Epidemiology**

The prevalence of angina pectoris is not well known and most of the available studies are somewhat old. In a recent overview, it was estimated that the prevalence of angina ranged from 2% to 5% among men aged 45 to 54 and 11% to 20% in men aged 65 to 74. Figures in women of the same age were markedly lower, ranging from 0.5% to 1% and 10% to 14%, respectively. These figures highlight two key features of the epidemiology of angina: at a given age, it is far more prevalent among men than among women (except above 85 years old), and its prevalence increases markedly with age after 40 years of age. It is estimated that 2 million people suffer from angina in the United Kingdom.

Recent studies have highlighted a major change in the epidemiology of the disease in industrialized countries: with the improvement in preventive measures as well as in prognosis and survival after acute coronary events, the disease burden is shifting toward older age groups. Given the increasing age of the population in most Western countries, this is therefore likely to result in an increase in the overall prevalence of the disease. Indeed, recent statistics appear to confirm this: comparison of two British censuses of the prevalence of angina in England and Wales, collected in 1981-1982 and 1991-1992, re-

**Selected abbreviations and acronyms**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>ACTION</td>
<td>A Coronary disease Trial Investigating Outcome with Nifedipine GITS</td>
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<tr>
<td>CAD</td>
<td>coronary artery disease</td>
</tr>
<tr>
<td>CAPRIE</td>
<td>Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events</td>
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<tr>
<td>CARISA</td>
<td>Combination Assessment of Ranolazine in Stable Angina</td>
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<tr>
<td>EUROPA</td>
<td>EUropean trial on Reduction Of cardiac events with Perindopril in patients with stable coronary Artery disease</td>
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<tr>
<td>HOPE</td>
<td>Heart Outcomes Prevention Evaluation</td>
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<td>HPS</td>
<td>Heart Protection Study</td>
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<tr>
<td>IONA</td>
<td>Impact On Nicorandil in Angina</td>
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<tr>
<td>MI</td>
<td>myocardial infarction</td>
</tr>
<tr>
<td>PCI</td>
<td>percutaneous coronary intervention</td>
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<td>RITA</td>
<td>Randomized Intervention Trial of Angina</td>
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Stable angina treatment in the 21st century: what is still missing?  
by P. G. Steg, France

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Keywords: stable angina; epidemiology; treatment; angiotensin-converting enzyme inhibitor; β-blocker; antiplatelet; statin; aspirin; percutaneous coronary intervention; secondary prevention; evidence-based medicine

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respectively, demonstrates an overall 60% increase in the prevalence of (International Classification of Diseases) ICD-9 code 413, with an almost doubling of the prevalence in patients aged 75 years or more (Figure 1).

Angina affects quality of life in all its dimensions, as demonstrated by a classic analysis from the Randomized Intervention Treatment of Angina (RITA) trial. In more than half of the patients, the severity of anginal symptoms seriously limits their everyday activities, often leading to premature retirement. Angina may also occur following an acute coronary event: from the Framingham data, it is estimated that approximately half of the patients who survive an acute MI suffer from residual angina.

The current therapeutic armamentarium for stable angina

- **Treatments to prevent death or MI**
  Most of these treatments do not have a direct anti-ischemic effect. There are essentially three categories of such therapies: antiplatelet agents, statins and angiotensin-converting enzyme (ACE) inhibitors.

- **Antiplatelet agents**
  They are of proven efficacy in preventing cardiac events and death in all forms of coronary heart disease: unstable angina, acute MI, and stable angina. A collaborative analysis of trials of antiplatelet agents showed a 22 per 1000 absolute reduction in the risk of adverse vascular events after 2 years of treatment in patients with stable angina. Thus, aspirin is widely recommended for patients with all forms of ischemic heart disease, including patients with stable angina, in the absence of contraindication. In patients who are intolerant or allergic to aspirin, thienopyridines—specifically, clopidogrel—may be an alternative therapy. Although there are no data available regarding the specific group of patients with stable angina, the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial suggests that, in secondary prevention of cardiovascular disease, this agent is at least as effective as aspirin.

- **Statins**
  There is solid evidence for a reduction in cardiovascular events with statin therapy in patients with elevated cholesterol. More recently, the Heart Protection Study (HPS) demonstrated that treatment with 40 mg of simvastatin was associated with a reduction in all-cause mortality in patients at high risk of cardiovascular events, including patients with “normal” lipid levels and with a substantial (odds ratio [OR] 0.76) reduction in the risk of any vascular event in patients with all forms of coronary heart disease. Therefore, aggressive lipid-lowering treatment should be initiated in patients with established coronary artery disease (CAD) such as stable angina.

- **ACE inhibitors**
  ACE-inhibitor therapy is of proven efficacy for treating hypertension and heart failure. The Heart Outcomes Prevention Evaluation (HOPE) trial established its benefits in 9297 patients at high risk of cardiovascular events, defined as patients: aged >55 years; with evidence of vascular disease or diabetes; plus one other cardiovascular risk factor; and who were not known to have a low ejection fraction or heart failure. In that trial, total mortality was reduced by 16% from 12.2% to 10.4% (P=0.006), and the composite primary end point of cardiovascular death, MI, or stroke was reduced from 17.7% to 14.1% (P=0.001). This was strongly suggestive of benefits beyond treatment of hypertension or heart failure. The European trial on Reduction Of cardiac events with Perindopril in patients with stable coronary Artery disease (EUROPA) was established to test the ability of perindopril to reduce cardiovascular death, MI, and cardiac arrest in patients with stable CAD and no clinical evidence of heart failure. After 4.2 years of follow-up, patients randomly assigned to perindopril had a lower rate of cardiovascular death, MI, or cardiac arrest than patients randomized to placebo (8.0% vs 9.9%, P=0.0003). This was associated with a consistent benefit on secondary end points, notably the combined end point of total mortality, MI, unstable angina, and cardiac arrest (14.8 vs 17.1%, P=0.0009), which had been the original primary end point of the study. With respect to the primary end point of the study, approximately 50 patients must be treated for 4 years to prevent 1 major cardiovascular event. EUROPA confirms and extends the results seen in the HOPE trial. In aggregate, these two trials strongly suggest that all patients with CAD should receive perindopril 8 mg or ramipril 10 mg daily.

- **Medical therapy to relieve ischemia and symptoms**
  There are various classes of agents available to control or prevent myocardial ischemia and anginal symptoms in patients with CAD, including β-blockers, calcium channel blockers, nitrates and nitrates-like agents (eg, molsidomine), metabolic agents (eg, trimetazidine or ranolazine), and potassium channel blockers (eg, nicorandil). It is generally estimated that these agents have a similar efficacy against angina (judged from the number of angina crises or the use of rapid-acting nitrates) or against ischemia (judged from the duration of exercise on a stress test). Yet, most of these agents have not been proven to reduce morbidity-mortality in patients with angina, largely because of the small number
of trials performed and because of the low background rate of events in patients with stable CAD.

**β-Blockers**

β-Blockers represent the cornerstone of anti-ischemic therapy for stable effort angina (in patients with pure rest angina related to coronary spasm with angiographically normal coronary arteries, β-blockers are ineffective and may in fact exacerbate symptoms by resulting in unopposed α-receptor activation).10

The benefit of β-blockers may very well extend beyond their ability to control anginal symptoms, and the survival benefit of secondary prevention with β-blockers after MI11 or in the treatment of hypertension suggests that they might be effective in preventing recurrent episodes of instability and MI. Finally, considering the role of the sympathetic nervous system in the triggering or facilitation of severe ventricular tachyaryrthmias and sudden death, it is logical that β-blockers may also be beneficial to patients with stable angina by preventing ventricular arrhythmias or sudden death.

**Calcium blockers**

As a class, calcium antagonists appear very similar to β-blockers in relieving anginal symptoms in chronic stable angina.9 These agents have been shown to be very effective in reducing angina in patients with vasospastic angina. Yet, their impact on patient outcomes has been the subject of intense debate: some,12 but not all analyses of retrospective case-control studies in hypertensive patients have shown increased risks of MI with calcium antagonists, mostly with immediate or short-acting dihydropyridines. The 2002 American College of Cardiology/American Heart Association (ACC/AHA) updated guidelines for the management of chronic stable angina indicate that relatively short-acting dihydropyridine calcium antagonists have the potential to enhance the risk of adverse cardiac events and should be avoided, while long-acting calcium antagonists, including slow-release and long-acting dihydropyridines and nondihydropyridines are effective in relieving symptoms and should be used in combination with β-blockers if they are not sufficient, or a substitute when they are contraindicated or have unacceptable side effects.7 Recently, ACTION (A Coronary Disease Trial Investigating Outcome with Nifedipine gastrointestinal therapeutic system [GITS]) has compared the long-acting GITS formulation of nifedipine with placebo.13 This is in contrast to previous studies that have used short-acting formulations of nifedipine. Just under 8000 patients were followed for a mean of 4.9 years — half of whom were treated with nifedipine GITS and half with placebo. The primary end point was major cardiovascular event-free survival, defined as time to occurrence of any of the following events: death from any cause, acute MI, refractory angina, new overt heart failure, dehildating stroke, and peripheral revascularization. Among patients allocated to nifedipine, 310 died (1.64 per 100 patient-years) compared with 291 people allocated to placebo (1.53 per 100 patient-years, P=0.41). Primary end point rates were 4.60 per 100 patient-years for nifedipine and 4.75 per 100 patient-years for placebo (P=0.54). With nifedipine, the rate of death and any cardiovascular event or procedure was 9.32 per 100 patient-years versus 10.50 per 100 patient-years for placebo (P=0.0012). The difference was mainly attributable to a reduction in the soft end point of “need for coronary angiography and interventions” in patients assigned to nifedipine, despite an increase in peripheral revascularization. Nifedipine had no effect on the rate of MI. Considering that this study compares nifedipine with placebo, these data do not make a compelling case for adding nifedipine to the treatment of patients. They suggest that long-acting nifedipine is probably safe in the context of stable angina, but, conversely, does not have a benefit in terms of reduction of “hard” end points.

**Nitrates**

Nitrates are highly effective in relieving anginal symptoms, being most frequently used as short-acting sublingual spray or tablet preparations. In addition, transdermal or oral long-acting nitrates also prevent ischemic episodes and anginal recurrences. Despite their unequivocal efficacy in curing or preventing anginal attacks, no outcome studies have been performed to demonstrate the benefit of nitrates on clinical outcomes in stable angina. Thus, presently, this class of agents is mostly indicated for symptom relief and prevention, alone or in addition to β-blockers or calcium blockers.

**Nicorandil**

Nicorandil is a potassium channel activator that has pharmacologic properties similar to those of nitrates and appears effective in the treatment of stable angina. In addition to its anti-ischemic properties, this agent may have cardioprotective effects related to mimicking the myocardial preconditioning effect. The Impact On Nicorandil in Angina (IONA) trial14 has demonstrated, in patients with stable angina, that nicorandil was associated with a reduction in the combined end point of coronary heart disease death, nonfatal MI, or unplanned hospitalization for cardiac chest pain after a mean follow-up of 1.6 years (15.5% vs 13.1% in the placebo and nicorandil groups, respectively; P=0.014). The trial did not demonstrate a reduction in mortality or combined mortality and nonfatal MI.

**Metabolic agents**

Trimetazidine has been shown, in several double-blind randomized trials, to improve exercise capacity and anginal symptoms.15-18 These symptomatic benefits are equivalent to those of propranolol19 or nifedipine20 and additive with those of diltiazem21,22 or metoprolol.23 Ranolazine (not yet available for clinical use in any country), was recently shown to be effective in improving symptoms in patients with chronic stable angina, in the recent Combination Assessment of Ranolazine in Stable Angina (CARISA) placebo-controlled randomized trial.24,25 However, for both of these agents, no benefit on clinical outcomes has been demonstrated yet.

Unmet medical needs

Given this host of available therapies to treat symptoms and ischemia, what is really missing in our management of these patients?
stable angina and $I_F$ inhibition: new insights and applications

- Need for effective treatments with fewer side effects
- Need for improved safety and tolerability of antianginal agents

Current antianginal agents almost all have frequent and sometimes severe side effects, most of which are related to their hemodynamic impact. Even side effects considered as relatively mild (e.g., headaches with nitrates or leg edemas with calcium blockers), although of course not life-threatening, are certainly common causes for treatment discontinuations, and it is well known that compliance judged from

<table>
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<tr>
<th>Table I. The most common reasons why further revascularization procedures are not possible.</th>
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<td><strong>Reasons for not performing revascularization in chronic stable angina</strong></td>
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<tr>
<td>1. Unsuitable anatomy</td>
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<td>2. Previous CAGBs or PTCA which exclude further revascularization</td>
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<td>3. Lack of graft material</td>
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<td>4. Impaired left ventricular function in patients with previous CAGB and/or PTCA</td>
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<tr>
<td>5. Extraocular disease which increase peri/post operative morbidity or mortality</td>
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<tr>
<td>6. Age — often in combination with the aforementioned factors</td>
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the selected population participating in clinical trials overestimates what is seen in “real life” in unselected patients. The problem of side effects assumes even greater proportions given the frequency of “combination therapy” using several anti-ischemic agents to prevent or control ischemic symptoms. In that case, side effects such as hypotension, leg edema, and negative inotropy become much more frequent.

- Need for more effective antianginal agents

Because patients sometimes have refractory angina. Apart from the issues of safety and tolerability of current antianginal agents, efficacy remains often insufficient. Some patients are resistant to antianginal therapy and have refractory angina. This is not an uncommon problem: although figures are lacking to assess the size of the problem, there is no doubt that there are patients with severe disabling angina and CAD who are refractory to conventional forms of treatment, even used in combination. A recent European Society of Cardiology (ESC) Joint Study Group report has reviewed this issue and detailed the potential therapeutic options in patients with refractory angina. These treatments are often largely experimental. Options include (but are not limited to) enhanced external counterpulsation, laser myocardial revascularization, coronary angiogenic therapy, neuremodulation techniques (using transcatheter electric nerve stimulation and spinal cord stimulation), or even thoracic epidural anesthesia.

- Because patients may not be amenable to revascularization.

There is a temptation to think that given the tremendous advances in percutaneous and surgical myocardial revascularization, the issue of chronic stable angina is dwindling. This is in fact far from true. Given the increasing lifespan of patients with established CAD, they will often experience acute coronary events, revascularization, and stable angina, albeit at different times. Often, angina persists despite or after revascularization has already been performed and the conundrum is whether or not to attempt further revascularization. There is a host of reasons to forego revascularization, listed in Table I. In fact, a Swedish survey of patients referred for angiography because of severe angina pectoris in 1994-1995 found that 6% to 9% of patients referred for revascularization were rejected despite severe symptoms.26

- Because revascularization does not always abolish myocardial ischemia, anginal symptoms, or the need for antianginal therapy. One would like to think that after myocardial revascularization, be it surgical or percutaneous, both anginal symptoms and myocardial ischemia are abolished and that patients are no longer at risk of adverse cardiac events. However, studies demonstrate the opposite, even after successful revascularization for stable angina, a condition theoretically rather at low-risk of acute events. Myocardial ischemia often persists after revascularization, and in the majority of cases is silent.27 Data from the National Heart, Lung, and Blood Institute (NHLBI) Dynamic Registry, which enrolled 1755 consecutive percutaneous coronary intervention (PCI) patients in 1997 (of whom 26% with angina in the previous 6 weeks), shows that 1 year later, event rates were high, and higher among patients with more severe angina prior to revascularization (Figure 2A).28 These data also demonstrate that the combined prevalence of angina and events was superior to 18% (Figure 2B).29 Finally, the use of antiischemial medications was needed in a substantial number of patients, even when they were symptom-free: more than 60% of the patients were on beta-blockers and roughly one third of patients were taking at least one other antianginal. Even allowing for the indication of beta-blockers after acute MI, these figures demonstrate the relatively frequent need for antianginal therapy in patients having undergone successful contemporary percutaneous revascularization.24 In another study using systematic myocardial perfusion assessment following PCI, 19% of patients complained of angina after PCI and 32% had evidence of ischemia on perfusion imaging.27 Silent ischemia impacted negatively on outcomes, but symptomatic ischemia was associated with a very high rate (52%) of critical events at follow-up (Figure 3).27

- Because antianginal therapy is more difficult in some patient subsets. A good example is patients with angina pectoris and congestive heart failure, who represent a difficult group to treat. While their prognosis is far more severe than that of same-age patients with angina, treatment options are often limited in this group. In the context of acute heart failure, it is impossible to institute beta-blockers or other negative inotropic antianginal agents, and it is usually necessary to discontinue them if they were previously prescribed. Therefore, in that context, nitrates and nitrate-like agents are often the only anti-ischemic therapy that can be used. In fact, despite the overall frank clinical benefit of beta-block-
controlled trials. There is thus a dire need for more evidence of improved clinical outcomes with anti-ischemic agents. Since the extent and severity of ischemia are directly related to prognosis in patients with CAD, it might be hoped that anti-ischemic agents would be helpful in improving prognosis. Yet, very few trials have suggested or demonstrated a potential clinical benefit on “hard outcomes” such as death or MI solely from antianginal agents, in the context of stable angina, largely because of the lack of placebo-controlled trials. There is thus a dire need for more trials in appropriate, and particularly in older, high-risk patient populations to test and demonstrate that outcomes can really be improved with antianginal agents.

Need for better implementation of evidence-based therapies
There is clear evidence from the recent literature that despite the availability of effective and proven therapies, these are not always used in “real-life” situations. Studies have shown that “undertreatment” with evidence-based therapies is associated with worse outcomes. Specifically, patients with CAD clearly benefit from therapy using the “fab four” combination of antiplatelet agents, β-blockers, statins, and aspirin, and, recently, increased mortality has been associated with underprescription of this combination in patients with acute coronary syndromes. This has prompted efforts to improve adherence to guidelines and use of evidence-based therapies. Stable angina is one area where much remains to be done in that respect.

Need for improved secondary prevention and lifestyle modification
Apart from the use of antianginal agents, evidence-based therapies also encompass other areas such as secondary prevention and lifestyle interventions.

![Figure 2](image-url)

**Figure 2.** Event rates 1 year after successful percutaneous revascularization in the National Heart, Lung, and Blood Institute (NHLBI) Dynamic Registry, as a function of the severity of anginal symptoms prior to PTCA. A: adverse cardiac event rates. B: Combined incidence of angina and events.

**Abbreviations:** CAGB, coronary artery bypass grafting; CCS, Canadian Cardiovascular Society (classification); MI, myocardial infarction; PCI, percutaneous coronary intervention.


![Figure 3](image-url)

**Figure 3.** Prognostic impact of ischemia 6 months after myocardial perfusion scintigraphy. PCI, percutaneous coronary intervention.


Clearly, more needs to be done to address the issue of continued smoking in patients with CAD and the growing problems of obesity, metabolic syndrome, and diabetes, which are harbingers of future trouble for these patients.

**Conclusion**
In conclusion, stable angina is frequent and impacts on outcomes and quality of life. Many patients are not amenable to revascularization and many suffer from angina despite proper medical therapy. Others may have symptoms despite having had revascularization. Current medical therapy has shortcomings, mainly related to insufficient efficacy, lack of hemodynamic tolerance, and side effects. There is currently little proof of a direct impact of anti-ischemic therapy on clinical outcomes in the context of stable angina. Finally, better implementation of evidence-based medicine and improved secondary prevention are issues “of the future” in the 21st century.

Stable angina treatment in the 21st century: what is still missing? – Steg
Stable angina and IPR Inhibition: New Insights and Applications

TRAITEMENT DE L’ANGOR STABLE AU XXIe SIÈCLE : QUE MANQUE-T-IL ENCORE ?

Un vaste arsenal thérapeutique est de nos jours disponible pour les cliniciens confrontés au traitement de l’angor stable. Celui-ci inclut des agents anti-ischemiques efficaces ainsi que d’autres traitements qui semblent capables de prêcher l’apparition d’événements cardiovasculaires adverses. En outre, l’utilisation des techniques de revascularisation myocardique a connu un développement considérable, en particulier au travers de l’émergence – et désormais de la prééminence – des techniques d’intervention coronarienne percutanée, qui ont nettement pris le pas sur la revascularisation chirurgicale. Et pourtant, en dépit de ces remarquables avancées, il demeure de nombreux besoins non satisfaits dans le domaine du traitement des patients souffrant d’angine de poitrine. Aussi, en ce début du XXIe siècle, de nombreux défis restent à relever, tels que le développement de traitements plus efficaces assortis d’effets adverses moins nombreux, la confirmation de l’amélioration des critères cliniques d’efficacité, une meilleure mise en œuvre des traitements issus de la médecine basée sur les faits (evidence-based medicine), et l’amélioration de la prévention secondaire et de l’hygiène de vie.
Common wisdom has it that myocardial ischemia is characterized by an imbalance between supply and demand,1 and that increased heart rate contributes to such imbalance by both decreasing supply and increasing demand. This view, though not incorrect, is too simplistic, largely because it does not adequately consider the regional nature of myocardial ischemia2 in most clinical scenarios, except cardioplegic arrest, where, however, heart rate is of no importance.

This review will therefore start out by characterizing in detail both the supply side and the demand side of regional myocardial ischemia and will then proceed to analyze the impact of heart rate thereon. Finally, the benefits resulting from pharmacological heart rate reduction will be presented and the potential advantage of selective bradycardic agents over β-blockers highlighted.

Methods for the quantitative analysis of regional myocardial blood flow and contractile function

Myocardial blood flow (perfusion)

At the experimental level, the gold standard for the measurement of regional myocardial blood flow is the microsphere method.3 This technique has a spatial resolution down to below 100 mg of myocardial tissue, depending on the number of injected microspheres.4,5 At this spatial resolution, myocardial blood flow, even during normoperfusion, displays a sizeable heterogeneity, with some areas having a mean blood flow of less than 20% and others of more than 200%.6,7 This spatial heterogeneity of myocardial blood flow is associated with a similar heterogeneity in oxidative metabolism8-10 and protein expression.11 Whether or not contractile func-
tion is similarly heterogeneous at the microregional level is entirely unclear at present (see below). The major limitation of the microsphere technique is the restricted availability of radioactive or color tracers. As a result, only a limited number of sequential measurements can be made and continuous recording of regional blood flow is impossible. Clinically, the only available method to measure regional myocardial blood flow quantitatively is positron emission tomography (PET). However, in addition to the high cost of technical requirements and the concerns relative to radiation safety that prevent its widespread and frequent use, PET has serious limitations. PET flow measurements lack sufficient spatial—particularly transmural—resolution, and the lack of respiration and/or cardiac motion-gated measurements enhances this problem, such that the spatial resolution is approximately 1 to 2 orders of magnitude less than that of the microsphere technique (ie, 1 to 10 g rather than 100 mg of myocardium). Also, the very few reported normal blood flow values from healthy volunteers vary widely, ie, from 0.68±0.16 [SD] mL·g⁻¹·min⁻¹ to 1.02±0.25 mL·g⁻¹·min⁻¹. As a result, in an individual patient, a major reduction in resting blood flow may go undetected, while an only modest reduction in transmural blood flow evidenced by PET in regions with contractile dysfunction may well translate into a much more severe reduction in subendocardial blood flow, the latter being the primary determinant of transmural wall function. Finally, PET, as the microsphere technique, permits no continuous monitoring of myocardial blood flow, and most studies only report data at one single time point.

**Myocardial contractile function (contraction)**

At the experimental level, the gold standard for the measurement of regional contractile function is sonomicrometry of either segment shortening or wall thickening. One major advantage of sonomicrometry, in contrast to the above flow measurement techniques, is that it permits continuous monitoring of contractile function. Its spatial resolution, however, is less than that of the microsphere technique, possibly by about 1 order of magnitude, although sonomicrometry can quantify differences between base and apex and, especially, between subendocardial and subepicardial contractile function. Also, sonomicrometry measures only wall excursion, but not wall stress. As severely hypokinetic and akinetic myocardium may be subjected to sizeable wall stress, this means that the extent of contractile function and its associated metabolic cost are largely underestimated by sonomicrometric measurements of wall excursion only. This consideration must be borne in mind, particularly when equating perfusion-contraction matching with energetic supply-demand.

Clinical methods to measure regional contractile function include echocardiography, contrast ventriculography, radionuclide ventriculography, and magnetic resonance tomography. Like sonomicrometry, these clinical techniques fail to take into account wall stress. For obvious reasons, continuous measurements of regional contractile function, although technically possible with echocardiography, are not available.

Considering the technical limitations outlined above, it is immediately apparent that no combination of techniques to measure regional myocardial blood flow and function has the spatial and temporal resolution to truly quantify the time course of their relation during the development of myocardial ischemia.

**Quantitative relationship between perfusion and contraction in normal and ischemic myocardium**

**Normoperfusion**

In the normal heart, increases in contractile function are associated with increased metabolism, and increased metabolic demand is met principally by increased myocardial blood flow and, to a lesser extent, by increased oxygen extraction. The mechanisms/mediators of such metabolic coronary dilation are still unclear; however, this is clearly a situation of perfusion-contraction matching, where alterations in contractile function are the cause of alterations in blood flow. Whether or not perfusion-contraction matching holds also true at the microregional level, ie, whether or not the substantial spatial heterogeneity of myocardial blood flow is associated with a similar spatial heterogeneity of myocardial blood flow, the latter being the primary determinant of transmural wall function, is still unclear due to the insufficient spatial resolution of current techniques to measure contractile function. A reverse causal relationship, ie, increases in myocardial blood flow causing increases in contractile function, does not exist in the normal beating heart.

**Acute ischemia**

Upon acute coronary artery inflow reduction, contractile function in the ischemic region is rapidly decreased. As soon as a steady state has developed (2 to 3 min) enabling the measurement of regional myocardial blood flow with the microsphere technique, a consistent, close relationship to the reduced regional contractile function is apparent. In 1980, Vatner was the first to demonstrate an exponential relationship between subendocardial blood flow and subendocardial segment shortening. Subsequently, Weintraub et al characterized the relationship between subendocardial blood flow and subendocardial segment shortening as sigmoidal and Galagher et al showed that the relationship between systolic wall thickening and subendocardial or transmural blood flow was more or less linear (Figure 1). Whereas the shape of this flow/function relationship has been a matter of some controversy in the past, at present, the consistent, close perfusion-contraction matching appears more important than subtle differences in the shape of such relationship, which may be attributable to differences in experimental conditions, segment shortening vs wall thickening, data presentation, and statistical phenomena. The relationship between ischemic regional myocardial blood flow and con-
Heart rate reduction in acute myocardial infarction – Heusch and Schulz


Figure 2. Collateral (left) and transmural (right) steal phenomena. P1= pressure at the origin of collaterals, P2= pressure at the orifice of collaterals into the ischemic terminal vascular bed. F1= flow through the stenosis, F2= collateral blood flow. Any dilation of the normal terminal vascular bed will decrease P1, and, as a consequence, the P1-P2 gradient, and finally P2. Reproduced from reference 49: Baumgart D, Ehring T, Krajaar M, Heusch G. A proischemic action of nisoldipine: relationship to a decrease in perfusion pressure and comparison to dipyridamole. Cardiovasc Res. 1993;27:1254-1259. Copyright © 1993, Elsevier, Ltd.

Distribution of perfusion and contraction in ischemic and nonischemic myocardium

Perfusion

Whereas collaterals obviously have a cardioprotective function, they can also be the underlying morphological substrate for an aggravation of myocardial ischemia when steal phenomena occur. In the presence of a flow-limiting coronary stenosis, flow into the ischemic terminal vascular bed is the sum of coronary arterial inflow through the stenosis and of collateral inflow from adjacent nonischemic or less ischemic regions (Figure 2). Collateral inflow is dependent on the pressure gradient between the origin of collaterals in the intact donor vessels and their orifice in the ischemic recipient vessels. When the dilator reserve of the ischemic recipient vessels is fully exhausted and flow is therefore pressure-dependent, any dilation of the nonischemic donor terminal vascular bed during enhanced metabolic demand or in response to dilator agents will decrease the driving pressure gradient across the collateral and, as a consequence, collateral flow. This phenomenon has been termed collateral steal. A similar situation arises with respect to the transmural distribution of myocardial blood flow when subendocardial autoregulatory reserve is exhausted, but some subepicardial autoregulatory reserve persists. The dilation of subepicardial vessels during enhanced metabolic demand will then compromise subendocardial perfusion, a phenomenon termed transmural steal. A transmural steal phenomenon can be considered as the major cause of the preferential subendocardial manifestation of myocardial ischemia and infarction. Finally, a steal situation also develops when a stenotic coronary artery perfuses parts of both the left and right ventricle. During increased myocardial metabolic demand, redistribution from the left to the right ventricular perfusion territory, ie, a right ventricular steal phenomenon, may occur. The presence of a well-developed collateral circulation often maintains sufficient blood flow to the poststenotic myocardial at rest, but steal phenomena contribute to the precipitation of myocardial ischemia during exercise.
**Contraction**

In addition to regional ischemic dysfunction, outlined above, regional myocardial ischemia also impacts on the nonischemic myocardium. During acute coronary artery occlusion in anesthetized swine and in both anesthetized and conscious dogs, the ischemic region is surrounded by a narrow zone of normally perfused myocardium with depressed systolic wall thickening or segment shortening. This depressed contractile function in the immediate borderzone surrounding the ischemic region is attributed to more or less well-defined mechanical “tethering” between nonischemic and ischemic myocardial fibers. The mechanism of such “tethering” is likely explained by the existence of high regional wall stresses present at the border between ischemic and dysfunctional vs normal myocardium. This dysfunctional borderzone leads to overestimation of the ischemic region from a diagnostic point of view.

A dysfunctional nonischemic borderzone may not only extend laterally from an ischemic region during complete coronary occlusion, but may also overly the ischemic inner myocardial layers during nontransmural ischemia. The subepicardium was shown to become dysfunctional when ischemia is restricted to the subendocardium and subepicardial perfusion is normal and outer wall dysfunction was found to be out of proportion to the outer wall flow reduction during treadmill exercise in dogs with coronary stenosis.

Whereas lateral and transmural tethering create a nonischemic dysfunctional borderzone in the immediate vicinity of the ischemic region, more remote nonischemic regions are characterized by enhanced contractile function. Whether an increase in remote nonischemic zone function can be considered as compensatory in that it acts to preserve global left ventricular function is not completely clear, since a major proportion of nonischemic zone hyperfunction occurs during isovolumic systole and does not contribute to ejection. The increase in function in the remote nonischemic zone is associated with a moderate, presumably metabolically mediated increase in blood flow to this region. However, the relationship between regional myocardial blood flow and function in remote, hyperfunctioning, nonischemic myocardium has not yet been systematically analyzed.

**Effects of heart rate on perfusion and contraction in normal and ischemic myocardium**

Increases in heart rate increase the number of cardiac cycles per time frame and thus also increase the energy/oxygen demand per time frame (Figure 3). Also, in some species, possibly including man, increases in heart rate increase the myocardial inotropic state through a force-frequency effect. With an intact coronary circulation, metabolic vasodilation serves to increase coronary blood flow to match the increased oxygen demand, since myocardial oxygen extraction is near-maximal at baseline and can only be increased by a small amount. Simultaneously with increasing oxygen demand, increases in heart rate also shorten diastolic duration and thus the time interval of the cardiac cycle during which almost all of coronary blood flow occurs. In an intact coronary circulation, metabolic vasodilation is powerful enough to overcome the limitation of coronary blood flow due to reduced diastolic duration so that the increased oxygen demand is adequately matched; thus, increases in heart rate are associated with proportionately increased myocardial oxygen consumption. However, in the presence of severe coronary stenosis, when the autoregulatory capacity of the coronary circulation to maintain a normal coronary blood flow at baseline is exhausted, any further increase in heart rate, more precisely, any further reduction in diastolic perfusion time, compromises coronary blood flow to the point where it is actually reduced at higher heart rates.

In the setting of regional myocardial ischemia, in cases where a severely stenotic coronary artery is connected via collaterals to an intact or less severely affected coronary artery, a typical redistribution/steal scenario develops, as outlined above: metabolic vasodilation of the more or less intact coronary microcirculation decreases collateral perfusion pressure, thereby decreasing collateral blood flow in the poststenotic coronary microcirculation and precipitating ischemia. In addition to the steal phenomenon, the hemodynamic severity of a coronary stenosis is increased at higher heart rates because of increased turbulence, further compromising coronary inflow.

**β-Adrenergic blockade in regional myocardial ischemia**

Exercise and excitement are characterized by sympathetic activation, and β-adrenergic mechanisms contribute to myocardial ischemia through an unfavorable redistribution of coronary blood flow away from the ischemic subendocardium, i.e., through both a collateral as well as a transmural steal mechanism (see above). β-Blockade decreases heart rate at rest and attenuates the exercise-induced increas-
es in heart rate, left ventricular dP/dt, and function of the nonischemic myocardium. As a consequence, increase in blood flow to the nonischemic myocardium and to the poststenotic subepicardium is attenuated. However, subendocardial blood flow of the ischemic myocardium is increased, thus resulting in improved regional myocardial function. The hemodynamic severity of a dynamic coronary stenosis is reduced by β-blockade. The β-blockade–induced autoregulatory decrease in flow to nonischemic regions results in an increase in poststenotic coronary perfusion pressure. Increased perfusion pressure, in turn, reduces stenotic resistance, thus ultimately improving blood flow to ischemic regions. The beneficial effects of β-blockade in exercise-induced myocardial ischemia are almost exclusively due to the attenuation of the increase in heart rate. When reduction in heart rate is prevented by atrial pacing, ischemic regional myocardial blood flow and function are even slightly reduced as compared with the untreated situation, possibly due to an unmasking of α-adrenergic constriction in the ischemic coronary microcirculation. The disadvantage of β-blockade in reducing the inotropic state is well appreciated; however, the importance of α-adrenergic coronary vasoconstriction in patients with stable angina or in patients undergoing coronary interventions has been largely neglected or underestimated so far.

**Selective bradycardic agents in regional myocardial ischemia**

The finding that β-blockade not only reduces heart rate, but also the myocardial inotropic state, and that it unmasks α-adrenergic coronary vasoconstriction, has prompted the development of selective bradycardic agents. Selective bradycardic agents are chemically distinct compounds; the first drug that was advocated in the early eighties as a selective bradycardic agent was alinidine. Alinidine’s promotion as a selective bradycardic agent coincided with the detection of the sinoatrial pacemaker current (I$_s$) by DiFrancesco. The I$_s$ current subsequently became the target of all selective bradycardic agents, including the clonidine derivative alinidine, the benzazepinones UL-FS 49 and ivabradine, and others. In conscious chronically instrumented dogs with a coronary stenosis, alinidine reduced heart rate both at rest and during treadmill exercise. The ischemic contractile dysfunction that developed during exercise was attenuated, but this was at the expense of a significant negative inotropic effect, both at rest and during exercise. Also, in anesthetized pigs, alinidine decreased heart rate, caused a favorable redistribution of myocardial blood flow into the poststenotic subendocardium, and attenuated ischemic contractile dysfunction, but again at the expense of a negative inotropic action. Alinidine has also been used in patients with acute myocardial infarction and appeared to be safe, though it was without effect in terms of myocardial salvage and arrhythmias.

UL-FS 49 also decreased heart rate, both at rest and during exercise, in conscious chronically instrumented dogs with coronary stenosis. It improved poststenotic subendocardial blood flow and attenuated ischemic contractile dysfunction, and these beneficial effects were achieved in the absence of negative inotropic actions. Subsequently, the mechanism of the beneficial action of UL-FS 49 in acute myocardial ischemia was analyzed in more detail and plots of contractile function vs subendocardial blood flow (Figure 4) were established in anesthetized pigs. UL-FS 49 improved regional systolic wall thickening for any given subendocardial blood, when expressed in conventional terms as blood flow per minute. However, when blood flow was expressed as blood flow per cardiac cycle and thus normalized for the same time frame as contractile function (see above), the flow/function relationships at different heart rates became superimposable, indicating that the beneficial effect of UL-FS 49 on ischemic regional myocardial blood flow and function was indeed entirely mediated through heart rate reduction. With UL-FS 49, a more favorable blood flow distribution into the left ventricular subendocardium occurred not only from the left ventricular subepicardium, but also from...
the right ventricle, ie, there were reverse transmu-
ral and interventricular steal phenomena.

Given these beneficial effects on ischemic myocardial blood
flow and its distribution, it is not surprising that
UL-FS 49 also decreased infarct size during more
prolonged ischemia in anesthetized pigs, as did atenolol; how-
ever, contractile function was better preserved with UL-FS 49 than with atenolol.58 De-
spite its favorable anti-ischemic profile, UL-FS 49 was
never further developed for clinical use.

The only currently available selective brady-
cardic agent approved for clinical use is ivabradine
(S 16257). In conscious chronically instrumented
dogs, ivabradine causes a dose-dependent reduction
in heart rate at rest and during exercise, and—in
contrast to propranolol—exerts its effects without
a negative inotropic action. Furthermore, ivabra-
dine only slightly attenuates the increase in epi-
cardial coronary artery diameter during exercise,
whereas propranolol actually reduces epicardial
diameter, thus unmasking α-adrenergic coronary
vasoconstriction (Figure 5).106 Accordingly, ivabra-
dine prolongs diastolic duration (thereby increasing
perfusion) and reduces myocardial oxygen con-
sumption (demand).101,102 In chronically instrument-
ed dogs with a coronary stenosis, ivabradine again
reduced heart rate at rest and during treadmill ex-
ercise and, as UL-FS 49, improved poststenotic sub-
endocardial blood flow and contractile function.
These beneficial effects during exercise-induced is-
chemia were followed by an attenuation of postis-
chemic contractile dysfunction, ie, stunning, and
attenuation of both ischemic and postischemic
contractile function was lost when the reduction
in heart rate was eliminated by atrial pacing. In con-
trast, β-blockade with atenolol also attenuated is-
chemic contractile dysfunction, but not postischem-
ic stunning, and also reduced nonischemic wall
function.103,104

The attenuation of ischemic contractile dysfunc-
tion with reduced heart rate elicited by ivabradine
was confirmed in conscious pigs during treadmill
exercise. These animals also displayed less ST-seg-
ment shift, similar to the effects of propranolol, but
without the latter’s negative inotropic action.106 In
animal experimentation, ivabradine appears to ful-
fill all the criteria for selectively decreasing heart
rate without negative inotropic action and without
unmasking α-adrenergic coronary vasconstriction.
Ivabradine’s detailed effects on the flow/function
relationship (perfusion-contraction match) and on
infarct size during more prolonged ischemia have
not been elucidated yet.

Recently, preliminary clinical data on the effects
of ivabradine in patients with chronic stable angina
have become available. In a double-blind, placebo-
controlled prospective trial, patients receiving iva-
bradine had prolonged time to 1-mm ST-segment
depression (Figure 6)105 and angina during exercise
testing during 3 months of use, without any re-
bound during drug withdrawal.105 In a rat model of
post–myocardial infarction remodeling and heart
failure, ivabradine reduced end-diastolic LV volume,
but not end-diastolic LV volume, thereby increasing stroke
volume and preserving cardiac output.108 In patients
with left ventricular dysfunction, ivabradine also
reduced heart rate without any appreciable nega-
tive inotropic effect.108

In conclusion, increases in heart rate play a ma-
jor role in precipitating myocardial ischemia, pre-
dominantly through unfavorable blood flow redis-
brution away from the ischemic subendocardium.
Accordingly, selective heart rate reduction atten-
uates the reduction in both regional myocardial
blood flow and contractile function. Importantly,
this dual attenuation is achieved without triggering
a negative inotropic action or unmasking α-adren-
ergic coronary vasoconstriction.

Figure 5. Increases in epicardial coronary artery diameter with increasing intensity
of exercise (Ex5, Ex10, Ex12) with placebo (circles) are only slightly attenuated with
ivabradine (triangles), whereas with propranolol (squares) epicardial coronary artery
diameter is decreased. *P<0.01 vs saline; **P<0.01 vs baseline; †P<0.01 vs propranolol.

Figure 6. Changes in time to 1-mm ST-segment depression during exercise in patients
with chronic stable angina.
Reproduced from reference 106: Borer JS, Fox K, Jaillon P, Lerebours G. Antianginal and antiischemic
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Cette synthèse débute par l’étude détaillée de la relation quantitative qui existe entre le débit sanguin et la fonction contractile à l’échelon régional, au sein du myocarde normal et ischémique. Selon une notion commune, c’est un déséquilibre entre les apports et les besoins qui serait le principal mécanisme pathogénique à l’origine de l’ischémie myocardique. Cette analyse détaillée montre, bien au contraire, que la perfusion et la contraction sont en fait diminuées de manière proportionnelle, au point qu’il existe un équilibre entre l’une et l’autre. Ce couplage perfusion-contraction est également maintenu aux fréquences cardiaques élevées, quand la fonction contractile et le débit sanguin régional sont normalisés en fonction de la même échelle de temps, c’est-à-dire un cycle cardiaque. Dans le myocarde normal, la régulation du métabolisme prévaut et l’augmentation de la fréquence cardiaque s’accompagne d’un élévation du débit sanguin coronaire. En revanche, au sein du myocarde irrigué par une coronaire sténosée, alors que la réserve vasodilatatrice est limitée, c’est la réduction de la durée de la diastole qui prévaut et le débit sanguin coronaire diminue alors que la fréquence cardiaque augmente. Au sein de la microcirculation coronaire située en aval d’une sténose mais connectée par une circulation collatérale à un territoire vasculaire moins affecté, la conjonction de deux facteurs va diminuer la pression dans cette dernière et, de ce fait, le débit sanguin régional post-sténotique : d’une part, la vasodilatation métabolique au sein de la microcirculation plus ou moins normale, d’autre part, la diminution de la durée de la diastole. Une augmentation de la fréquence cardiaque, médiée par les récepteurs β-adrénergiques, est habituellement observée lors de l’activation sympathique qui survient à l’occasion d’un effort ou d’une émotion. De ce fait, les β-bloquants ont été utilisés dans le traitement de l’ischémie myocardique liée à l’effort. Cependant, les études qui ont abordé leurs mécanismes d’action ont révélé que les bénéfices induits par la réduction de la fréquence cardiaque étaient, en partie, contredits par un effet inotrope négatif et un démasquage de la vasoconstriction α-adrénergique. Des agents bradycardisants plus sélectifs ont été développés, qui diminuent sélectivement la fréquence cardiaque sans induire d’effet inotrope négatif et sans démasquer la vasoconstriction α-adrénergique. Ceux-ci augmentent la distribution du débit sanguin au sein du myocarde ischémique et, en conséquence, améliorent la fonction myocardique régionale. L’ivabradine est le seul agent bradycardisant sélectif disponible en clinique. Il a été récemment démontré que ce médicament exercerait une action anti-ischémique chez les malades atteints d’un angor chronique stable.
A ngina pectoris, a debilitating symptom of myocardial ischemia, can result from coronary artery occlusive disease. Though importantly limited in quality of life, most people with angina can expect excellent survival. Current drug therapy completely prevents angina only in a minority of patients, even when multidrug regimens are employed. Therefore, additional pharmacological alternatives are desirable, employing pharmacological effects different from those of conventional therapy. Myocardial ischemia results from imbalance between myocardial oxygen supply and demand. Limitation of heart rate, a primary determinant of demand, is particularly useful in angina prevention. The inward sodium-potassium-mediated If current of sinoatrial node cell membranes (virtually absent elsewhere in the myocardium), modulates sinoatrial diastolic rate and, thus, heart rate. Blockade of this current reduces heart rate. Icivabradine, a highly selective If current blocker comprising linked benzazepinone and benzocyclobutane rings, causes clinically useful heart rate decrements at doses that are generally well tolerated and virtually devoid of other cardiovascular effects; the only predictable (dose-related, ≤18% incidence at 10 mg PO twice daily) adverse effects are visual (photopsia, stroboscopic effect, nontypical blurred vision) that usually are only mildly bothersome, fully reversible with cessation of therapy, and not associated with retinal damage. Clinical trials involving >4000 patients indicate that icivabradine, as monotherapy, is effective in preventing angina. Effects are seen in doses as low as 2.5 mg twice daily; when employed at 7.5 mg or 10 mg twice daily, angina prevention with icivabradine is equivalent to that achieved with amlodipine 10 mg daily or atenolol 100 mg daily.

Keywords: stable angina; If current; heart rate reduction; treatment; icivabradine

I_{f} inhibition as a therapeutic approach in stable angina: experimental and clinical studies

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creasing the duration of mechanical diastole. Additionally, though unlikely to affect typical effort-induced angina (a condition associated with relative stability of the atherosclerotic plaque), heart rate slowing should minimize risk of plaque disruption (and acute ischemic events) by reducing mechanical perturbation of the plaque caused by fore-shortening and twisting of large epicardial arteries during systole. Counterbalancing these potentially beneficial effects, heart rate slowing limits cardiac output at rest and cardiac output reserve; in certain individuals, this can result in unacceptable fatigability. However, the clinical impact of these effects cannot be predicted a priori: reduction in ischemia may enhance exercise tolerance beyond the effect of cardiac output limitation. Indeed, prevention of ischemia may prevent myocardial dysfunction that could limit output more than heart rate reduction.

Experimental and clinical data indicate that heart rate slowing is an important part of the antianginal, anti-ischemic effects of several commonly employed drugs, including β-adrenergic blockers and calcium channel blockers of the verapamil and diltiazem types. However, these drugs have pharmacological effects in addition to heart rate slowing, including negative inotropic activity (both β-blockers and calcium channel blockers) and peripheral vasodilatation (calcium channel blockers), the latter often associated with blood pressure reduction; in theory, these effects can add to antianginal efficacy, but can also cause debilitating “side effects.”

Nonpharmacological heart rate slowing was achieved three decades ago with direct electrical stimulation of the carotid sinus. The method was effective in preventing angina, but the procedure itself and discomfort associated with the use of the implanted stimulator limited its application. Therefore, pure heart rate slowing by pharmacological means, with agents devoid of additional, potentially deleterious properties, has remained a goal of drug research.

**I<sub>f</sub> current blockers: experimental and clinical pharmacology**

More than three decades ago, the theoretical benefits of pure heart rate slowing led to initiation of efforts to develop selective sinus node inhibitors without direct effects on other cardiac electrophysiological properties or on myocardial mechanical function or peripheral vascular tone. The role of the hyperpolarization-activated mixed sodium-potassium inward (I<sub>f</sub>) current in generating spontaneous activity in cardiac pacemaker cells was first elucidated shortly thereafter; subsequent further characterization identified a clear target for drug-mediated heart rate slowing. The first I<sub>f</sub> current blocker tested clinically as an antianginal was UL-FS 49. However, despite promising preclinical findings and antiangina prevention was not achieved with the doses employed clinically, despite some heart rate reduction both at rest and during exercise. Additional testing, using higher and possibly more effective doses, was not undertaken because transient ocular toxicity was observed at the initially employed doses. The adverse visual effects have been attributed to inhibition of currents in the retina similar to those in the sinoatrial node.

Though UL-FS 49 failed in clinical testing, I<sub>f</sub> current inhibitors with other molecular structures were evaluated for more favorable therapeutic-toxic ratio. More than a decade ago, ivabradine, with I<sub>f</sub> current-blocking activity, was reported to have pharmacological properties that compared favorably with UL-FS 49. Ivabradine, which structurally comprises linked benzazepinone and benzocyclobutane rings, is highly selective for the I<sub>f</sub> current. Preclinical studies indicated that heart rate slowing could be achieved with ivabradine in a dose-dependent manner without affecting myocardial contractility, peripheral vascular resistance, coronary vascular resistance, and mean arterial pressure, without changing the myocardial oxygen delivery–to–myocardial oxygen consumption ratio. Ivabradine also did not affect electrocardiographic PR and QT intervals, whereas, experimentally, UL-FS 49, less specific for I<sub>f</sub> than ivabradine, caused QTc prolongation. The lack of QTc prolongation by ivabradine is noteworthy because such electrophysiological alteration is a potent risk factor for clinically important ventricular arrhythmias that had marred research with early selective sinus node blockers. In other preclinical studies, ivabradine minimized exercise-induced ischemia and stunning and, at doses causing heart rate slowing comparable to that of the β-blocker atenolol at rest and during exercise, ivabradine depressed myocardial relaxation modestly and less than the β-blocker, suggesting a potential advantage for the pure heart rate–slowing I<sub>f</sub> inhibitor.

In clinical trials, at the doses most commonly employed (5-10 mg twice daily), ivabradine has consistently demonstrated heart rate reduction at rest and during exercise of the same magnitude as is effected by commonly employed doses of β-blocking drugs, but without alteration in blood pressure (and other cardiovascular functional changes) commonly seen with β-blockers. Thus, when compared with placebo at peak exercise, ivabradine 10 mg twice daily resulted in almost 15 beats/min lower heart rate at trough of drug activity; the heart rate response was dose-related, with evidence of a heart rate–lowering effect even at the lowest dose tested (2.5 mg twice daily). When compared directly with the β-blocker atenolol, heart rate lowering with ivabradine 10 mg twice daily was only modestly less than that with atenolol 100 mg daily (though antianginal effects of these doses were similar, as discussed below). Despite substantial heart rate lowering, ivabradine caused little change in blood pressure relative to placebo, and caused modestly less blood pressure lowering than atenolol.

**I<sub>f</sub> current blockers: antianginal efficacy and safety from clinical trials**

To date, ivabradine has been studied in controlled clinical trials involving more than 4000 patients with coronary artery disease and chronic stable an-
Stable angina and \( I_f \) inhibition: New insights and applications

**Figure 1.** Changes in heart rate (bpm, beats per minute) at rest (A) and at peak exercise (B) in the different treatment groups during the double-blinded, dose-ranging phase of the ivabradine trial. Error bars, standard error of the mean.

*P*<0.05 versus placebo in pairwise comparison.


Most trials have maintained active treatment for at least 3 months (the generally accepted minimum duration of studies employed for purposes of approval for marketing by legally constituted regulatory authorities). This is the largest antianginal drug development program yet recorded. The results of these studies support the efficacy of ivabradine for prevention of exertional angina and the underlying ischemia; adverse effects have been acceptably mild, so that the drug is likely to be tolerable in clinical practice.

By consensus within the regulatory and research communities, the primary evidentiary standard for antianginal efficacy is improvement in exercise tolerance on standard treadmill or bicycle ergometric testing. This should be supplemented by evidence of reduction in associated exercise-induced ischemia to preclude the possibility that treatment is “masking” angina by an analgesic effect, which might allow patients to exercise unwittingly to severe and potentially lethal ischemia without symptomatic warning. Angina frequency with ambient activity, as recorded in diaries, is considered adjunctive evidence, but is not dispositive because the intensity of stress inciting ambient angina in daily living cannot be determined from diary reports. Drug effectiveness should be demonstrable at the end of the interdose interval (“trough”), not only at the time of maximal drug effect (“peak”).

Any standard method (exercise electrocardiography, myocardial perfusion scintigraphy, radionuclide cineangiography, stress echocardiography) can be employed to demonstrate anti-ischemic effect, though, in practice, this is done most easily and economically by assessing time to 0.1 mV (1 mm) ST-segment depression during the standardized exercise test with and without treatment.

\( I_f \) current blockade with ivabradine has been evaluated for antianginal/anti-ischemic effect in comparison with placebo in the absence of any other chronic (“background”) therapy, in comparison with placebo on a background of amiodipine administered to patients with and without ivabradine, and in direct comparison with atenolol and with amiodipine. The latter two studies were designed to test “noninferiority” of ivabradine versus standard antianginal therapies. In the context of these studies, “noninferiority” is a statistical concept aimed at determining the consistency with which, for a prespecified outcome variable, one intervention fails to differ from another by more than an amount agreed, a priori, to be of no clinical importance. Other definitions exist, but depend upon existence of a wellcharacterized and statistically stable magnitude of incremental effect of the comparator therapy versus placebo known from previously reported trials; such stable placebo-controlled “point estimates” do not exist for antianginal drugs.

**Placebo-controlled monotherapy**

The efficacy of ivabradine was first confirmed in a large (n=360 patients) double-blind, placebo-controlled, multicenter, multinational study (Figure 2), in which patients were randomized to receive either ivabradine 2.5 mg PO twice daily, 5 mg PO twice daily, or 10 mg PO twice daily, or placebo, for 2 weeks (“dose ranging”). Then, in an open-label extension, the dose was increased to 10 mg PO twice daily for 2 to 3 months (in those who accepted continuation and for whom local regulations permitted such extension). At the conclusion of the open-label phase, randomized, double-blinded withdrawal to placebo was undertaken in half the population, while the other half was randomized to maintain treatment with 10 mg PO twice daily. After exclusion of 103 patients who withdrew from treatment or violated protocol constraints, results were analyzed among the 257 patients treated according to protocol. Compared with placebo, time to limiting angina increased nominally at all doses, reaching statistical significance at ivabradine 10 mg twice daily. When responses to all doses were considered, a dose-effect relation was apparent and a between-group comparison was statistically significant (\( P = 0.049 \)). When protocol violators were included in the analysis (“intention-to-treat” population), ivabradine remained superior to placebo at trough when 10 mg was administered twice daily, though the difference...
Time to 1-mm ST-segment depression was significantly reduced by ivabradine 5 mg bid and 10 mg bid, and a significant dose-response relation was seen across all doses for this effect, indicating that angina prevention was associated with an anti-ischemic effect.16 Diary recordings and tabulation of short-acting nitroglycerin use indicated that angina attack rate and nitroglycerin use during routine daily living was lower at the end of the protocol than at pretreatment baseline among patients receiving ivabradine, and increased among those randomly withdrawn to placebo at the end of the open-label treatment phase, while remaining unchanged during randomized withdrawal, time to limiting angina fell significantly in patients withdrawn to placebo, but remained unchanged in patients maintained on ivabradine 10 mg twice daily (between-group difference: \(P=0.018\), Table I, page 42).16
 Investigators. Anti-anginal and anti-ischemic effects of ivabradine, an 

Figure 3. Changes in time to 1-mm ST-segment depression and limiting angina in patients receiving ivabradine 10 mg bid (n=59) or placebo (n=65) during the randomized withdrawal phase of the ivabradine trial. *P<0.05 versus ivabradine.


<table>
<thead>
<tr>
<th>Parameter</th>
<th>Ivabradine 10 mg bid</th>
<th>Placebo</th>
<th>Between-group P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate at rest (bpm)</td>
<td>-0.44 ±5.6</td>
<td>13.3 ±8.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Maximal heart rate (bpm)</td>
<td>-1.31 ±7.48</td>
<td>12.3 ±8.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time to 1-mm ST-segment depression (s)</td>
<td>4.25 ±59.7</td>
<td>-32.0 ±73.7</td>
<td>0.003</td>
</tr>
<tr>
<td>Time to limiting angina (s)</td>
<td>-0.78 ±48.8</td>
<td>-25.2 ±63.9</td>
<td>0.018</td>
</tr>
<tr>
<td>Time to angina onset (s)</td>
<td>2.1 ±59.1</td>
<td>-36.0 ±76.7</td>
<td>0.002</td>
</tr>
<tr>
<td>RPP at rest (bpm-mm Hg)</td>
<td>-26.0 ±1207</td>
<td>1487 ±1628</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RPP at peak of exercise (bpm-mm Hg)</td>
<td>-180 ±3195</td>
<td>1813 ±3331</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Expressed as value at end of the randomized withdrawal phase minus value at end of the open-label extension phase.

Table I. Changes in ETT parameters, measured at trough of drug activity, during the randomized withdrawal phase.*

Abbreviations: RPP: rate pressure product.


This trial also indicated the relative safety of ivabradine use during a 3-month treatment interval. Adverse events were relatively few and generally similar in frequency and distribution compared with placebo, except for visual symptoms (photopsia, stroboscopic effect, nontypical blurred vision). Visual symptoms were dose-related, rarely sufficiently bothersome to cause voluntary withdrawal from the drug, and invariably reversible with drug cessation, consistent with the absence of irreversible retinal effects reported in preclinical studies. Visual side effects occurred in approximately 15% of subjects at 10 mg twice daily during the dose-ranging phase and 18% during the open-label phase. Since the sinoatrial node is the target of I\textsubscript{f} blocking therapy, patients with disease of this structure (eg, “sick sinus syndrome”) were excluded from ivabradine trials and, in the current state of our knowledge, should not receive this drug. With this caveat and exclusion, neither syncope nor untoward hypotension nor heart failure was associated with ivabradine administration in the placebo-controlled trial of the drug as monotherapy, nor in the other large clinical trials described below. Note, of course, that ivabradine would be ineffective in patients chronically in atrial fibrillation since the drug does not affect the atrioventricular node and, therefore, cannot modulate heart rate in these patients.

Direct comparisons with approved antianginal drugs at commonly employed doses

In 1195 patients randomized to ivabradine 7.5 mg twice daily or amlodipine 10 mg daily, a 3-month multicenter, multinational, double-blind study demonstrated that ivabradine was indistinguishable from amlodipine in its effects on total exercise duration, time to limiting angina, time to angina onset, and time to 1-mm ST-segment depression. Formal statistical testing of data from this as yet unpublished trial revealed ivabradine to be noninferior to amlodipine (P=0.0001 for this conclusion).

In a 4-month double-blind study, 939 patients were randomized, first, to ivabradine 5 mg twice daily or atenolol 50 mg daily for 2 weeks; then, doses were uptitrated to ivabradine 7.5 mg or 10 mg twice daily or to atenolol 100 mg daily. No statistically significant differences were found when various outcomes were compared among the tested regimens at each stage, and ivabradine’s noninferiority to atenolol was significantly established at the doses employed (P<0.0001). However, despite the fact that atenolol 100 mg daily resulted in slightly greater heart rate reduction than with either ivabradine 7.5 mg or 10 mg twice daily, ivabradine was nominally superior to atenolol in enhancing time to angina onset, time to limiting angina, and total exercise duration at all doses, while time to 1-mm ST-segment depression was virtually identical among the regimens. This finding suggests that pharmacological effects of β-blockers other than heart rate slowing may impact negatively on the pathophysiology of angina. This hypothesis remains to be rigorously tested.
Stable Angina and \( I_f \) Inhibition: New Insights and Applications

Conclusions

A growing body of data indicates that angina and the underlying ischemia can be effectively minimized using selective sinoatrial node \( I_f \) current blockade to slow heart rate. These data also suggest that, when this effect is achieved with ivabradine, effective prevention of angina is associated with acceptable safety and tolerability.

Because of the relatively high prevalence of angina within the world’s population (discussed elsewhere in this issue), the availability of a new approach to angina prevention has important public health implications. Currently available drug therapy with single or multiple agents often fails to completely or optimally prevent angina. Indeed, recent data indicate that a substantial majority of patients with angina receive combination antianginal therapy involving at least two drugs, but, nonetheless, continue to experience approximately two angina attacks per week. Availability of a new agent, with pharmacological effects different from currently available drugs, may enhance the rate of therapeutic success. Also, since drugs with different pharmacological profiles are likely to differ also in frequency, character, and distribution of adverse effects, tolerability of treatment across large populations is likely to be enhanced by availability of an additional drug that may be tolerable when others are not. For example, \( \beta \)-blockers may potentiate the symptoms of peripheral arterial occlusive disease (commonly associated with coronary artery disease) or obstructive pulmonary diseases, while increasing the risk of untoward events in patients with hypertension or intrinsic atrioventricular node disease, and possibly complicating the management of metabolic disorders (diabetes mellitus or hyperlipidemias). Certain calcium channel blockers (as well as \( \beta \)-blockers in some settings) can precipitate or potentiate congestive heart failure or atrioventricular node dysfunction; calcium channel blockers also frequently cause unacceptable peripheral edema and constipation (the latter particularly in elderly patients). The third most commonly used group of angina-preventing drugs, long-acting nitrates, can be nontolerated because of associated headaches or lightheadedness (which are, in fact, direct results of its beneficial pharmacological effects); intermittent use of these drugs may result in rebound angina and vasoconstriction. Albeit rarely, nitrates have resulted in methemoglobinemia when moderate overdoses are administered; it is even possible that nitrates may affect matrix metalloproteinase activity, potentially destabilizing atherosclerotic plaques.

These adverse effects are not expected with \( I_f \) current inhibition and, specifically, have not been associated with ivabradine use. Similarly, as demonstrated in preclinical studies (supplemented by as yet unpublished experience in patients with heart failure and with left ventricular ejection fraction <40%), \( I_f \) current inhibition with ivabradine does not suppress myocardial inotropy (potentially a problem with \( \beta \)-blockers and certain calcium channel blockers), is not associated with the potentially lethal “rebound” effects seen with abrupt cessation of short-acting \( \beta \)-blockers, and, as demonstrated by the results of randomized withdrawal after 2 to 3 months of treatment, does not result in pharmacological tolerance to its therapeutic effects when administered continually over a protracted interval, a problem previously identified when long-acting nitrates are employed.

Finally, in addition to symptom reduction and consequent quality of life enhancement that can be expected from ivabradine-mediated \( I_f \) current inhibition, it is possible that heart rate reduction may improve survival. Though the latter hypothesis remains to be tested in a large clinical trial, pharmacological heart rate slowing has been associated with mortality reduction in patients with heart failure and after myocardial infarction; drug-associated cardioacceleration has been associated with deleterious outcomes. Indeed, both actuarial data and observational studies in cohorts with a variety of cardiovascular and metabolic diseases, in the population at large, indicate a significant relation between casually measured heart rate and survival. The intriguing potential for survival enhancement in ivabradine with patients in coronary artery disease and, indeed, in other settings as well, remains to be explored.

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-effects of beta blockade.


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L’inhibition du courant I<sub>β</sub> en tant qu’approche thérapeutique de l’angor stable : Études expérimentales et cliniques

L’angor, qui est le symptôme le plus débilitant de l’ischémie myocardique, peut résulter d’une maladie coronaire obstructive. Même si l’angor limite notablement la qualité de vie, le plus souvent les malades concernés ont une excellente survie. Les traitements médicamenteux actuels ne préviennent totalement les crises d’angor que chez une minorité de sujets, même quand ils sont utilisés en association. Des alternatives pharmacologiques faisant appel à des propriétés pharmacologiques qui diffèrent de celles mises en jeu dans les traitements conventionnels sont donc souhaitables. L’ischémie myocardique résulte d’un déséquilibre entre les apports et les besoins en oxygène. La limitation de la fréquence cardiaque, un déterminant primaire des besoins en oxy-
gène, s’avère particulièrement utile dans la prévention de l’angor. Le courant entrant I<sub>β</sub>, Na<sup>+</sup> et K<sup>-</sup> dépendant, prévient au niveau des membranes cellulaires du nœud sino-auriculaire (alors qu’il est pratiquement totalement absent au niveau du reste du myocarde) module la fréquence diastolique sino-auriculaire, et, de ce fait, la fréquence cardiaque. L’inhibition de ce courant réduit cette derniè
er. L’ivabradine, un inhibiteur hautement sélectif du courant I<sub>β</sub>, qui associe un cycle benzazépinone et un cycle benzo(cyclobutane, induit une diminu-
fraction de la fréquence cardiaque qui s’avère cliniquement utile à des doses qui sont en général bien tolérées et pratiquement dénuées de tout autre effet car-
diovasculaire. Les seuls événements indésirables prévisibles (dose-dépendants, fréquence ≤18 % à la dose de 20 mg par jour en deux prises orales) sont visuels, à type de photopsie, d’effet stroboscopique et de vision floue atypique). Ces ef-
fets, habituellement légers et peu gênants, disparaissent complètement à l’ar-
rêt du traitement. Ils ne s’associent à aucune lésion rétinienne. Les essais clini-
qués qui ont inclus au total plus de 4000 malades indiquent que l’ivabradine en monothérapie est efficace dans la prévention des crises d’angor. Cet effet est percep-
tible dès les doses les plus faibles, en l’occurrence 5 mg/jour en deux prises. Aux doses de 15 et 20 mg/jour, toujours réparties en deux prises, la pré-
vention de l’angor est assurée avec une efficacité qui rejoint celle obtenue avec l’amiodarine (10 mg/j) ou l’aténolol (100 mg/j).
Selective and specific \(I_f\) inhibition: new perspectives

by H. Purcell and K. Fox, United Kingdom

Heart rate, along with preload, afterload, and myocardial contractility, are among the major factors that regulate cardiac pump function. Heart rate is also a primary determinant of oxygen consumption. This is particularly relevant in patients with coronary heart disease, when increases in heart rate and reduction in oxygen supply, in tandem with decreased time for myocardial relaxation and diastolic ventricular filling, can lead to development of myocardial ischemia. There is an inverse relationship between heart rate and life expectancy. The resting rate is an independent predictor of cardiovascular morbidity and mortality (see reviews, references 1,2). This is particularly marked in patients with unstable angina or acute myocardial infarction. A recent analysis3 looked at initial (day 1) hospital admission and delayed (days 2-3) heart rates in over 10 000 patients with acute coronary syndromes enrolled into a large clinical trial of an oral glycoprotein IIb/IIIa inhibitor. Findings showed significant greater 30-day and 10-month mortality among patients with higher initial and delayed heart rates. A number of possible reasons have been proposed to explain this, and why, clinically, tachycardia at rest is an adverse finding. Sinus tachycardia can reflect overactive sympathetic activity. It can be demonstrated experimentally that relatively high heart rates can amplify atherogenesis and endothelial dysfunction selectively in the coronary vessels, and that low heart rates can exert a sparing effect.

One classic experiment4 in cynomolgus monkeys fed a high cholesterol diet for 6 months, showed that after sinus node ablation by electrocautery, to reduce heart rate, coronary atheroma was twice as severe in the animals with higher heart rates who underwent a sham surgical procedure compared with those who had the ablation performed (55.9% vs 26.1% stenosis in the two groups, respectively; \(P<0.002\)). Similar findings were also seen with further work in carotid vessels. In both sets of experiments the animals did not significantly differ in blood pressure, serum lipids, or body weight.

In a study of 56 patients who had sustained a myocardial infarction (MI) before the age of 45 years and who underwent two coronary angiograms within a period of 4 to 7 years,5 progression of disease was predicted independently by heart rate. When patients were divided into high and low heart rate groups (by median value of minimum heart rate) coronary atherosclerosis progression was two times higher in the high heart rate group. A further retrospective study examined the relationship between bradycardia and the development of coronary collateral vessels on angiography in patients with obstructive coronary artery disease (CAD). Patel and coworkers observed that a larger number of pa-
Selective and specific \( I_f \) inhibition: new insights and applications

<table>
<thead>
<tr>
<th>EFFECT</th>
<th>COMMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bradycardia</td>
<td>Absolute contraindication in 2nd and 3rd degree heart block. Caution with other heart rate-lowering agents</td>
</tr>
<tr>
<td>Hypotension</td>
<td>May be exacerbated when used with potent vasodilators</td>
</tr>
<tr>
<td>Reduced contractility (negative inotropism)</td>
<td>Because of myocardial depression, initiate with caution in stable heart failure. Avoid in worsening unstable heart failure</td>
</tr>
<tr>
<td>Bronchospasm</td>
<td>May precipitate (life-threatening) asthma. Avoid in those with history of asthma or COAD, or use cardioselective agent with extreme (supervised) caution</td>
</tr>
<tr>
<td>Cold extremities</td>
<td>May be less common in agents with partial agonism. Avoid in Raynaud’s disease</td>
</tr>
<tr>
<td>Lethargy/fatigue</td>
<td>May adversely affect compliance</td>
</tr>
<tr>
<td>Nightmares/sleep disturbances</td>
<td>May relate to lipophilicity. Possibly reduced with hydrophilic agents, eg, atenolol</td>
</tr>
<tr>
<td>Inhibition of metabolic/autonomic responses to hypoglycemia</td>
<td>May mask symptoms of hypoglycemia in insulin-treated diabetics. Avoid in those with frequent hypoglycemia or taking sulfonylureas</td>
</tr>
<tr>
<td>Impotence/reduced sexual activity</td>
<td>Likely to be more common when ( \beta )-blockers used with thiazide diuretics. Generally not commonly reported in monotherapy trials</td>
</tr>
</tbody>
</table>

Table I. Effects that may limit or contraindicate use of \( \beta \)-blocker drugs. Abbreviation: COAD, chronic obstructive airways disease.

With heart rates \( \leq 50 \) beats/min had significantly greater development of collateral vessels (decreasing the ischemic burden) compared with control patients with heart rates \( \geq 50 \) beats/min, \( P<0.001 \). The presence of collaterals was independently the most widely prescribed of the heart rate–lowering drugs, there are differences between them, and some 20% of patients do not respond to any \( \beta \)-blocker. Similarly, there are well-documented effects with this drug class, which limit their use in terms of absolute or relative contraindications (Table I).

Development of sinus node inhibitors

While the interest in developing “specific bradycardic-agents” extends back over 50 years, the early 1970s saw the beginning of a formal research program. The hypothesis was that pure bradycardic agents could selectively reduce heart rate without affecting myocardial contractility, conductivity velocity and refractoriness, or arterial blood pressure. Drugs that act specifically to block the pacemaker current might allow an opportunity to see whether “isolated” heart rate reduction could alleviate ischemia by reducing myocardial oxygen consumption as well as by increasing the duration of myocardial perfusion. They might also be better tolerated and have potential to retard development of atherosclerosis and exert antiarrhythmic actions to prevent arrhythmia. A number of compounds were developed including falipamil, which were benzolactam derivatives of verapamil. This reduced heart rate experimentally, but was shown to produce QT prolongation, and it was therefore modified structurally to produce UL-FS 49, which was more specific, and potent and had a longer duration of action. While UL-FS 49 reduced heart rate to the same extent as propranolol, it also appeared to be anti-ischemic, it was found to provide no additional antianginal benefit in terms of greater exercise tolerance to patients already receiving nifedipine. UL-FS 49 has also been shown to cause QT prolongation and it causes dose-related ocular adverse effects, therefore it will not be developed for clinical use in the future.

Development of ivabradine

Ivabradine has been extensively investigated in recent years. Ivabradine is a novel, selective inhibitor of the cardiac pacemaker \( I_f \) current. The “funny” or “pacemaker” \( I_f \) current was described in pacemaker cells of the sinoatrial node as a current slowly activating on hyperpolarization that contributes to generation of cardiac rhythmic activity and its control by sympathetic innervation. Thus, the “funny” channels play a key role in generation of spontaneous activity of pacemaker cells and mediate autonomic control of heart rate. By increasing the duration of spontaneous depolarization it induces selective heart rate reduction. Ivabradine is a dextrorotatory isomer of the racemic compound that induces in animals and humans dose-dependent heart rate lowering, and that, because of its selectivity, has minimal effects on other myocardial tonic currents. The effects of ivabradine and propranolol have been compared in a pig model of exercise-induced myocardial ischemia. Both agents were equipotent in reducing heart rate at rest and limiting tachycardia on exercise. Ivabradine, unlike propranolol, did
not reduce left ventricular contractility at rest or during exercise and did not increase atrioventricular conduction time. Both compounds reduced exercise-induced ST segment shift in the ischemic region by about 80%, but only ivabradine preserved systolic shortening significantly, that is, β-blockade potentially limits the ability of the ischemic myocardium to respond to increased blood flow by increased contractile function. Further animal studies\textsuperscript{15} show that oral administration of ivabradine in mice reduces heart rate without influencing contractility and that this negative chronotropic effect is preserved even during significant (stress-evoked) activation of the sympathetic nervous system.

The degree to which reduction in heart rate and contractility respectively contribute to the beneficial effects of β-blockers remains debated. A recent study conducted in dogs attempted to dissociate these two factors.\textsuperscript{20} The study compared heart rate reduction during exercise-induced myocardial ischemia and stunning, with atenolol and ivabradine. Stunning is prolonged, but reversible, contractile dysfunction following acute ischemia despite the return of normal blood flow. Atenolol was shown to have greater effect on regional contractility (measured as a reduction in left ventricular wall thickening) when administered prior to exercise-induced ischemia, despite causing similar heart rate reduction to ivabradine. However, when administered after exercise, ivabradine attenuated stunning and shortened the recovery time for return to normal contractility (an effect that disappeared when heart rate reduction was reversed with atrial pacing), in contrast to atenolol, which did not. The authors suggest that selective heart rate reduction not only provides an anti-ischemic effect, but also improves contractility of the stunned myocardium, whereas additional negative inotropism is protective against ischemia, but deleterious in stunning. They argue then that ivabradine might be better as a first choice for angina pectoris.

### Clinical studies

The antianginal, anti-ischemic efficacy and safety of ivabradine have been assessed in a randomized, double-blind, placebo-controlled study of 360 patients with chronic stable exertional angina.\textsuperscript{11} All of the men and women enrolled (mean age about 58 years) had documented coronary artery disease. An initial 2- to 7-day washout period on placebo was followed by a 1-week, single-blind placebo-controlled run-in period. After this, patients were randomly assigned to placebo or ivabradine 2.5, 5, or 10 mg twice daily for 2 weeks, followed by a voluntary 2- or 3-month open-label extension phase during which all patients received ivabradine 10 mg twice daily to assess safety and maintenance of efficacy. Finally, those patients in the open-label extension were randomized to continue on ivabradine 10 mg twice daily or to withdraw to placebo for 1 additional week, in order to check for any rebound phenomena. Exercise tolerance tests (bicycle ergometry) were conducted on days 7, 0, and 14 at the trough of drug activity and day 14 at peak drug activity.

Ivabradine was well tolerated and no rebound phenomena were observed on drug withdrawal. A dose response in heart rate reduction was seen at all doses of ivabradine. Ivabradine 5 mg and 10 mg twice daily significantly increased time to 1-mm ST-segment depression ($P<0.0005$) and time to limiting angina on exercise. Patients continuing on ivabradine during the withdrawal period maintained improvements in exercise parameters, whereas there was significant deterioration with placebo. The incidence of overall side effects was low and similar between ivabradine and placebo. There was, however, a dose-related increase in visual disturbances (mainly photopsia) reported in 1 patient on ivabradine 2.5 and 5 mg and in 13 patients (14.8%) on ivabradine 10 mg twice daily. No visual disturbances were reported on placebo. All visual symptoms resolved spontaneously during or after drug discontinuation.

An extensive phase 3 program of clinical studies with ivabradine has been undertaken; this will be reviewed in detail elsewhere in this publication. Pivotal studies\textsuperscript{10} include a 3-month study in 1195 patients, where ivabradine 7.5 mg twice daily was found to have similar efficacy to amlodipine 10 mg once daily in increasing total exercise duration, time to limiting angina, time to onset of angina, and time to 1-mm ST-segment depression. Similarly, in a 4-month study in 939 patients comparing ivabradine 5 mg and atenolol 50 mg daily for 4 weeks, and then increased to 7.5 mg ivabradine or 10 mg twice daily with atenolol 100 mg daily, results confirmed the antianginal and anti-ischemic efficacy with all doses of ivabradine and demonstrated similar efficacy and safety with atenolol. These trials in chronic stable angina patients show that ivabradine significantly reduced the diary-recorded number of anginal attacks and reduced glyceryl trinitrate consumption by more than two thirds. Antianginal efficacy was consistently demonstrated, without the development of pharmacological tolerance or rebound.

An invasive clinical electrophysiology (EP) program has also been undertaken with ivabradine.\textsuperscript{19} Intravenous infusion of ivabradine 0.2 mg/kg in patients confirmed its heart rate–lowering properties and the absence of relevant influence on intra-atrial, atrioventricular, or intraventricular conduction times, and the absence of QTc prolongation. No effects on QTc or likelihood of proarrhythmia were observed with doses of ivabradine up to 20 mg twice daily. The compound was shown to be especially safe in studies conducted in patients with left ventricular dysfunction.

A further study\textsuperscript{20} is under way to assess the effects of chronic heart rate reduction with ivabradine in the prevention of atherosclerosis progression assessed using intravascular ultrasound (IVUS).

### Ivabradine in heart failure

Because of its lack of negative inotropism, ivabradine may be useful in controlling heart rate in patients with acute heart failure, treated with agents such as dobutamine, for example.\textsuperscript{21} Ivabradine was
investigated in a rat model of heart failure to determine the effects of long-term heart rate reduction on left ventricular (LV) function and remodeling. The study showed that in the animals who had experienced long-term (90 days) heart rate reduction following randomization to ivabradine, left ventricular function was improved relative to placebo, as stroke volume increased-preserving cardiac output. The investigators noted that this improvement in LV function was probably related not only to heart rate reduction, but also to modifications of left ventricular structure and/or myocyte properties. There was a decrease in LV collagen density and an increase in capillary density without any modification of LV weight, which persisted for at least 3 days after interruption of treatment with ivabradine.

One can only speculate about the mechanisms that contribute to modifications of myocardial structure and LV function. Possibly the heart rate lowering associated with ivabradine augments coronary perfusion, thus preventing development of endothelial dysfunction associated with local hypoxia and cytokine and free radical production. Similarly, it is not known whether such changes occur in clinical use. However, preliminary findings from trials suggest that myocardial contractility improves in patients with heart failure treated with ivabradine 10 mg twice daily over 3 months. Trials are planned to address this issue further.

Conclusions

Increased heart rate is an independent risk factor for development of ischemic cardiac events. Heart rate reduction with certain heart rate–lowering drugs, notably β-blockers in the post-myocardial infarction setting, can reduce this risk significantly. Specific bradycardic drugs, which are devoid of any hemodynamic effects other than heart rate lowering, have been shown to have anti-arrhythmic and anti-anginal properties. Ivabradine is a new and novel specific bradycardic agent, which acts by selectively inhibiting the pacemaker If current. It improves exercise parameters during exercise stress in patients with angina, compared with placebo. Ivabradine has comparable antianginal effects to atenolol and amlodipine. A large outcome study is now planned to examine the role of ivabradine in patients with LV dysfunction. Ivabradine is well tolerated and appears to be safe when used in clinical doses. The principal side effect, visual effects, is dose-related, and is experienced in a small percentage of patients, and reverses with discontinuation of drug use. Ivabradine does not appear to be proarrhythmic, and it may even improve cardiac function in patients with ventricular compromise. In summary, selective and specific If inhibition offers a new and exciting prospect for the future management of patients with ischemic heart disease.

REFERENCES

L'élévation de la fréquence cardiaque est associée à une augmentation du risque d événements cardio-vasculaires. Certains médicaments peuvent atténuer ce risque, c’est le cas, par exemple des bétabloquants dans le post-infarctus. Ces derniers ne sont pas cependant tolérés par tous les malades et leur effet inotrope négatif peut même contribuer à leurs effets indésirables.

De ce fait, le développement de nouveaux inhibiteurs du nœud sinusal dont les effets se limitent à la réduction de la fréquence cardiaque suscite un grand intérêt. L’un de ces agents bradycardisants spécifiques, l’ivabradine, est un inhibiteur sélectif du courant $I_f$ qui est le courant pacemaker primaire du nœud sino-auriculaire. Les effets anti-ischémiques et anti-angineux de l’ivabradine sont bien documentés. Du fait de son effet chronotrope négatif qui s’exerce sans que la contractilité soit altérée, ce médicament peut jouer un rôle important dans le traitement de l’insuffisance cardiaque. Plusieurs études sont en cours ou prévues pour étudier plus avant les propriétés de ce nouveau médicament.
CONTROVERSIAL QUESTION

Does gender influence the management of patients with stable angina?

1 R. Seabra-Gomes, Portugal

A quick answer to this question could be: it might, but... it shouldn’t. Women are considered to be protected from coronary artery disease (CAD) up to the age of menopause, with a 10-year delay of onset of symptoms and cardiovascular events compared with men. After that age, the incidence of CAD in women is similar to that of men. Mortality is 2.5 to 4.5 times lower in middle-aged women, but this difference decreases in the elderly subjects. Great emphasis has been placed over the past few years on the misdiagnosis and undertreatment of CAD in women. In fact, the number of deaths, mostly due to ischemic heart disease, has increased in women in the past decade, and this trend could continue due to the aging of the population and the epidemi-like incidence of obesity, metabolic syndrome, and diabetes, in women in particular.

There is no reason to believe that the same risk factors for CAD that are seen in men do not apply to women. Smoking habits, hypertension, high cholesterol, obesity, diabetes, metabolic syndrome, stress, sedentary lifestyle, etc, affect both women and men, and should all be taken into account for cardiovascular prevention in women. The real challenge is clinical diagnosis. Typical symptoms, such as chest discomfort or pain, are less frequent and more difficult to interpret in women, who also present with back and neck pain, indigestion, dizziness, fatigue, loss of appetite, or syncope. Our knowledge of the “female-pattern of angina,” which is distinct from that seen in men, is still incomplete, and this pattern may sometimes be confused with the most frequent comorbidities, particularly with increasing age.

Clinical decision-making is more difficult in women. In a recent meta-analysis to detect CAD in women, exercise testing (exercise ECG, thallium scintigraphy, and echocardiography) showed only moderate sensitivity and specificity for the diagnosis of CAD. More often, even in a symptomatic woman, the coronary angiogram is considered normal. This has led to the hypothesis that angina with normal coronary arteries is a benign situation and that CAD in women is a different disease, with a more prominent microvascular component.

However, 4-year risk-adjusted outcomes by extent of CAD in the Women’s Ischemia Syndrome Evaluation (WISE) study showed that there was a 9.4% death or myocardial infarction (MI) rate (or about 2.7% annually) in the subgroup with no or minimal disease on angiography. In an intravascular ultrasound (IVUS) substudy, >80% of women with so-called “normal angiograms” had plaque lesions and multiple lesions, and in a cohort that underwent acetylcholine coronary artery reactivity testing, women who failed to dilate had more cardiovascular events over follow-up, regardless of CAD severity. Women have ultimately poorer outcomes if they have CAD, with 1-year mortality rate about 1.5 times greater than in men. However, most differences in mortality for acute coronary syndromes or revascularization procedures are due to comorbid conditions and advanced age. If we all become aware that the risk of CAD in women is as important as in men, if we pay more attention to symptoms and noninvasive as well as invasive test findings, and if we consider that both revascularization strategies (percutaneous coronary intervention [PCI] or coronary artery bypass grafting [CABG]) should have the same indications irrespective of gender, prognosis in women would be the same as in men, paying special attention to the differences in comorbidities. Medical treatment remains the cornerstone of the management of stable angina. Once CAD is suspected or diagnosed, symptoms should be treated with the established pharmacological therapies available. According to the individual patient’s needs and tolerance, nitrates (I find the short-acting nitrates particularly useful for clinical diagnosis of angina-like symptoms), β-blockers, and calcium antagonists should be used for angina, and angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) (for those who are intolerant to the former) to block the multiple deleterious effects of angiotensin II. In the European trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease (EUROPA) trial, perindopril was equally effective in women in reducing cardiovascular death, acute myocardial infarction, and cardiac arrest. Anti-platelet therapy as well as statins should always be part of the medical regimen. Special attention should be paid to adequate and concomitant control of high blood pressure (more difficult in women), type 2 diabetes, depression, musculo-
Does gender influence the management of patients with stable angina?

CONTROVERSIAL QUESTION

8. D. Y. Hu and J. G. Yang, PR China

Chronic angina pectoris has detrimental effects on health-related quality of life, particularly in women. Research into gender difference in chronic angina pectoris suggests that women report greater functional disability related to angina symptoms. Clinical factors among women contributing to these gender differences include a delayed onset of disease, a tendency to present at an older age, and a higher prevalence of comorbidities at the time of presentation. Data from the Framingham study showed that angina pectoris is a more common clinical syndrome in women, contrasted with myocardial infarction (MI) and sudden cardiac death in men. This discrepancy may in part be due to an increased rate of atypical symptoms of angina pectoris in women compared with men. However, more women than men with chest pain clinically indistinguishable from angina have normal coronary arteries at arteriography. In the CASS Registry, 50% of women compared with 17% of men with a clinical history compatible with angina pectoris had no significant obstructive coronary artery disease (CAD). However, a majority of women without obstructive CAD at coronary angiography continue to have symptom-related disability and consume considerable health care resources, in part because the pathophysiology of ischemia in women is incompletely understood and gender-specific diagnostic and treatment strategies are underdeveloped. Therefore, women may be undertreated with effective therapies or often referred for care later than men, when their clinical status is more advanced. The higher risk of adverse outcomes associated with myocardial revascularization in women may be due to their greater likelihood of having severe disease. Whereas comorbid clinical conditions are known to contribute to the higher morbidity and mortality among women follow-
(eg, lesser in magnitude, limited to subendocardium, patchy distribution, prolonged duration) from those seen with a large-vessel obstruction. Endothelial dysfunction has been linked to oxidative stress resulting from many atherosclerosis risk factor conditions, particularly hypertension.

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Does gender influence the management of patients with stable angina?

It has been repeatedly documented that women with ischemic heart disease are investigated and treated less aggressively than men, although these differences have not been demonstrated in all studies. Women with ischemic heart disease present the same complications as men and their prognosis is similar or even worse that of men. Reasons for this possible bias have been a matter of controversy and clear recommendations have been made to improve the management of women with ischemic heart disease. Although this possible bias has been studied in different settings, including unstable angina, acute myocardial infarction, and chronic stable ischemic heart disease, very little information has been obtained in clinical trials and registries specifically focusing on patients with stable angina.

Is there evidence for gender bias in stable angina? One of the few registries in patients with stable angina addressing this problem is the Euro Heart Survey on Stable Angina (EuroHS-SA), recently presented during the last Congress of the European Society of Cardiology in Munich. In this multicenter survey, a total of 3900 patients, 42% women, were enrolled in 197 centers from 27 countries. Exercise stress testing and coronary angiography were less frequently performed in women than in men, and this difference was significant after adjusting for confounding factors such as age and functional class. Coronary angiography was less frequently used in women even after adjusting for the results of the exercise stress test. Treatment used in men and women was also different. Women received less frequently coronary revascularization and evidence-based-therapy, including antiplatelet and lipid-lowering drugs, but, on average, women received a greater number of antianginal medications.

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Does the different management have an impact on outcome? This is a difficult question that could not be properly answered only with the analysis of data from the limited number of patients included in the few registries of stable angina. Again, in the EuroHS-SA, 1-year outcome was similar in the overall study population of men and women, but women with stable angina and demonstrated coronary artery disease presented a higher 1-year mortality (odds ratio [OR] 1.5), almost double prevalence of myocardial infarction, and were less likely to report a complete control of angina symptoms than men. These findings highlight the importance of secondary prevention and treatment according to guidelines.

Why a gender bias?
A conscious bias is difficult to accept. Perception of a milder disease in women (by the physician and the patient herself), the more difficult clinical diagnosis due to different symptoms, the older age at symptoms presentation, and maybe lesser therapy compliance could in part explain the differences. However, at present, there is no clear explanation for the gender bias observed in patients with stable angina.

What can we do?
The diagnosis of coronary heart disease and its appropriate treatment may be more difficult in women presenting with chest pain, but this does not justify improper diagnosis and should not prevent appropriate treatment. The causes of chest pain should be investigated regardless of gender, secondary prevention counseling should be given according to guidelines, and treatment should be carefully monitored for efficacy to control ischemia. Finally, clinical research should be conducted for a better understanding of the possible reasons to explain the inappropriate treatment offered to women with stable angina and ischemic heart disease in general.
Despite recent advances in the management of coronary atherosclerosis, coronary artery disease (CAD) remains the first cause of mortality in women in the USA and the developed countries; it accounts for more than a quarter of a million deaths each year in the USA.\(^1\) The mortality rate in women after the first myocardial infarction is higher than in men,\(^2\) because of their more advanced age when the disease occurs, a higher prevalence of coronary risk factors and other associated comorbidities, as well as the smaller size and the higher tortuosity of their coronary arteries. In addition, women with acute coronary syndromes are less likely to benefit from cardiac procedures and new treatments.\(^3\) Most guidelines for the treatment of chronic stable angina do not include specific gender-related management.\(^4\) The class I pharmacotherapy to prevent myocardial infarction and death and to reduce symptoms, includes aspirin, \(\beta\)-blockers, long-acting nitrates, calcium antagonists (excluding short-acting dihydropyridines), angiotensin- converting enzyme (ACE) inhibitors in case of diabetes and/or left ventricular (LV) dysfunction, and statins if low-density lipoprotein (LDL) cholesterol is greater than \(\sim 130\) mg/dL, irrespective of gender. While the use of \(\beta\)-blockers is sometimes limited in young and middle-aged men because of sexual dysfunction, they should be widely prescribed in women in whom this problem does not occur. Clopidogrel could be an alternative choice when aspirin is contraindicated (class IIa). The recommendations for treatment of risk factors, as a preventive measure, are also identical in both sexes regarding the treatment of hypertension (according to the JNC 7 guidelines), diabetes and dyslipidemia, smoking cessation, weight reduction, and appropriate physical activity.\(^5\) Hormonal replacement therapy should be used with care in postmenopausal women as it has been associated in many cases with increased morbidity.\(^6,7\) Class I recommendations for revascularization with percutaneous coronary intervention (PCI) or surgery (coronary artery bypass grafting [CABG]) are also similar in both sexes:\(^8\) CABG is recommended for patients with significant left main coronary disease, 3-vessel disease mainly with abnormal LV function, 2-vessel disease with significant proximal left anterior descending coronary artery (LAD) and either abnormal LV function or demonstrable ischemia; either CABG or PCI can be performed for patients with 1- or 2-vessel disease without involvement of proximal LAD, but with a large area of viable myocardium, prior PCI and recurrent stenosis with viable myocardium, and in case of unsuccessful medical treatment with acceptable risk. In contrast, PCI alone is recommended for patients with 2- or 3-vessel disease with significant proximal LAD and suitable anatomy, normal LV function and no treated diabetes. Women are less likely to be referred for cardiac catheterization,\(^9\) but the rate of coronary revascularization (PCI, CABG) in stable angina seems to be the same as in men during the year after catheterization, and appears to reflect appropriate clinical decisions.\(^10\) Despite the fact that diabetes, hypertension, and hypercholesterolemia are more frequent in women with CAD, hospital mortality of CABG is not significantly different from men,\(^11\) except for younger women who seem to be at a higher risk of in-hospital death.\(^12\) On the other hand, off-pump CABG surgery may be better for women regarding the reduction of mortality, respiratory complications, and length-of-stay.\(^13\) Nevertheless, their outcome seems to be impaired after emergency CABG for failed PCI.\(^14\) Concerning PCI, the old data from the Nationwide Inpatient Sample confirm that female gender is an independent predictor of short-term mortality and CABG after the procedure.\(^15\) However, after the introduction of new stents with a lower profile and a higher tractability, the outcome has improved in women and became similar to men in more recent trials.\(^16,17\) Some controversies remain, however, regarding angiographic restenosis after stent implantation,\(^18,19\) with a strong impact of diabetes in most of the trials. Finally, when we compare CABG versus stenting for angina pectoris in women with multivessel disease in the Stent or Surgery (SoS) trial, both procedures appear equally effective after 1 year, although CABG was superior at 6 months.\(^20\) In conclusion, due to pathological comorbidities and unfavorable coronary anatomy, women with stable angina should be treated aggressively, either medically or surgically or by PCI. Comparatively to men, the diagnosis of CAD should be improved, and gender-based educational strategies and evidence-based guidelines for the treatment and the prevention of the disease should be implemented.\(^21,22\)
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cholersterol, lowers some coagulation factors (fibrinogen) while increasing others (factor VII). In observational studies, eg, the Nurses’ Health Study and Uppsala Study, hormone replacement therapy (HRT) lowered CAD risk. But prospective trials, eg, the Women’s Health Initiative (WHI)\(^2\) and the Heart and Estrogen/Progestin Replacement Study (HERS),\(^13\) failed to confirm benefit, while an initial mid-term decreased risk failed to persist at follow-up despite a 35% reduction in diabetes. HRT also conferred no benefit on atherosclerosis progression in angiographic CAD.\(^{14}\)

Women have higher levels of glutathione peroxidase 1, one of several cellular antioxidant enzymes that may protect against atherosclerosis.\(^{15}\) However, antioxidant vitamin supplementation combined with HRT had no benefit in postmenopausal women.\(^{16}\) Androgens may play an underestimated role in this regard, since hyperandrogenemia in men and hyperandrogenemia in women are associated with increased CAD; androgens also upregulate atherosclerosis-related genes in macrophages from males but not females. Estrogen receptor polymorphism is another factor accounting for the positive effects of estrogens in certain subgroups: the ER.alpha IVS1-401 C/C genotype is associated with an increased HDL response to estrogen,\(^{17}\) and the ESR 1c.A54-397 C/C genotype with an increased risk of infarction. Specific polymorphisms in eight genes are associated with a metabolic syndrome, with some gene associations being sex-specific. Sex bias affects some aspects of CAD management. Women are less likely to receive aspirin or aggressive lipid-lowering medication for secondary prevention in the primary care setting, but there is no bias in assessment and treatment by cardiologists or in revascularization rates.\(^{18}\) In very young women, percutaneous revascularization is followed by much higher rates of vascular complications, 1-year mortality, and q-wave infarction than in men.\(^{19}\) Bypass surgery is associated with more difficult recovery in women, independently of disease severity or prior health status; in women with angina, surgery is equal in efficacy to percutaneous stent-assisted intervention, while appearing superior in men with multivessel disease. Overall, women with CAD have a worse health-related quality of life outcome than men and a worse prognosis.\(^{20}\) Thus, women need aggressive primary and secondary prevention, together with appropriate prophylaxis for subgroups with unfavorable left ventricular hypertrophy.

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In one word, the answer is “yes.” However, it is of greater interest to discuss the origin of the difference. In my opinion, this is due to a series of facts and fancies. Until a few years ago, there was a broad consensus that coronary artery disease (CAD) had a lower incidence and carried a lesser risk in women than in men. It is true that CAD takes longer to appear in women (by approximately 10 years), but its incidence rapidly increases up until the age of 50 or 60 years, leveling off with men at age 75. Increased smoking and use of contraceptives over recent decades, together with an increased incidence of obesity and the metabolic syndrome, have favored an earlier appearance of the disease. In the world’s underdeveloped populations (more than 70% of humanity), there has been a decline in infant and juvenile mortality, and therefore more persons reach vulnerable ages for CAD. Improvements in factors such as malnutrition, the poor quality of water, the lack of sanitary and hygiene facilities, unsafe sex, and maternal and prenatal diseases have contributed to that achievement. It should also be recalled that myocardial ischemia symptoms in women are sometimes less characteristic than in men (back pain, nausea, fatigue, or abdominal pain, more prolonged angina crisis and a variable relationship with effort), thus making the initial diagnosis more difficult. As mentioned above, it was also thought that CAD carried a lesser risk in women. The initial manifestation of CAD in women is more often angina than acute myocardial infarction or sudden death. Furthermore, precordial pain in women may be due to various pathophysiological mechanisms not always linked to coronary atherosclerotic obstruction. For example, in women under 55, the association of angina and normal coronary arteries is more frequent. This difference may be explained by a range of disorders such as microcirculatory disorders, vasospasm, alterations in the threshold of pain, mitral valve prolapse, myocardopathies, panic attacks, costal chondritis, gastroesophageal reflexes, and many other less frequent causes (such as atroventricular fistulae). We have also observed hypochondriacs with totally atypical syndromes who after two or three medical consultations “learn” to report the classic syndrome. A well-directed interrogation is sufficient to put an end to the apparent illness. Other gender-related differences include the increase in smoking in women and a greater difficulty for them to quit the habit, and a greater difficulty to include women in long-term exercise programs. Another factor directly linked with gender is hormonal replacement therapy (HRT). The benefits of HRT (eg, decrease in incidence of hip fracture and colorectal cancer), should be balanced against the increased risk of stroke, pulmonary embolism, breast cancer, and, probably, CAD. The decision to give HRT should therefore be based on a strict individual benefit-risk evaluation, and it is advisable to prescribe HRT at the lowest dose and for the shortest duration possible. The alleged better evolution of CAD in women in fact disappears when populations of women with angiographically documented CAD are studied. Thus, if the natural evolution of CAD does not differ between men and women, treatment should be the same: this is not the case. Although several reasons may account for this paradox, the main cause of this difference in treatment appears to relate to the physician him/herself. Thus, for young patients, the Bayesian approach (pretest probability) indicates physicians have a positive predisposition toward the diagnosis of CAD for men, and a negative one for women. For elderly persons, less aggressive treatment in general is indicated, regardless of sex, in order to avoid drug interactions and to take account of differences in bioavailability (alterations in absorption and metabolism, and altered receptor sensitivity). Whatever the reason, women receive less pharmacological treatment (antiplalet drugs and β-blockers; also, certain risk factors are harder to treat in women). The percentage of women who undergo invasive procedures is also smaller, the causes again being diverse. The smaller number of angioplasties seems to be linked to a less prescription of angiographies; on the other hand it has been observed that no matter how high the number of angiographies is, the percentage of angioplasties almost always remains the same, which may reflect the differences in intervention criteria of each region or hospital. This highlights the difficulty in stratifying the clinical risk. In the case of bypass surgery, the explanation might be different; involving the reluctance to perform surgery in view of the clearly greater risk in women (due to higher average age, smaller body surface, and smaller coronary arteries). In conclusion, gender clearly exerts a strong influence on CAD management, due both to fact and fancy. As fancy give way to reality, CAD in women will increasingly be treated as seriously as in men.
After two studies 15 years ago identified differences between men and women in the delivery of heart disease care, it became clear that such differences also applied to diagnosis, treatment, and treatment response in angina. The reasons are multifactorial and continue to evolve. Elucidation must begin with a review of the evidence.

**Clinical evaluation and referral**
Chest pain is the most common presentation of angina, but nausea, shortness of breath, and atypical pain in the back, jaw, neck, or abdomen are more common in women. In premenopausal women, chest pain, whether typical or atypical, carries a lower risk of coronary artery disease (CAD) than in age-matched men, but the incidence of CAD increases after menopause. Even in acute myocardial infarction (MI), typical chest pain is less frequent than in men. Women with acute MI are older, with higher comorbidity (hypertension, diabetes). They also have a higher incidence of silent MI. A specific algorithm has been devised for managing women with angina and identifying the diagnostic tests and interpretations appropriate to those stratified into low, moderate, or high CAD probability based on chest pain characteristics and clinical risk factors; however, the investigations are based on the same indications as in men. Even in 2000, women—black women in particular—were less likely to be referred for cardiac catheterization. However, the most recent evidence indicates no such differences, but only a treatment difference, with percutaneous coronary interventions (PCI) being offered more often to women and surgery to men.

**Medical management**
MI is more often fatal in women, at both ends of the age spectrum, possibly due to later presentation to the emergency services and lower perceived risk by health care providers. Mortality remains higher for at least 2 years post-MI; morbidity—reinfarction, stroke, pulmonary edema, shock, and cardiac rupture—is also higher. All conventional drug therapies for angina and MI have well-established benefits in both genders, but are less used in women. Conventional therapy may also be less aggressive: despite an absence of gender bias in lipid assessment, distribution of lipid-lowering therapy, or proportion of patients achieving lipid targets, women were treated less aggressively in terms of absolute levels achieved.

**Revascularization**
- Percutaneous coronary intervention (PCI) PCI is less frequent in women, and registry data have suggested poorer results: the women had equivalent CAD, but were older, with more risk factors and more severe angina, resulting in higher complication and procedural mortality rates. Some construed this as evidence of female gender being an independent risk factor for major morbidity or mortality. But given comparable clinical severity and strict criteria for referral, catheterization and angioplasty, procedural referral rates have proven similar between the sexes, with similar rates of reocclusion, reinfarction, and mortality. PCI is equally effective in men and women. Female sex was actually an independent predictor of improved 5-year survival in the Bypass Angioplasty Revascularization Investigators (BARI) study.

- Coronary artery bypass grafting (CABG)
The morbidity and mortality of CABG have progressively declined, but remain 2 to 3 times higher in women, for reasons unresolved. As with PCI, women are older, with more comorbidity; they undergo less frequent distal anastomosis, left internal mammary artery grafting, complete arterial revascularization, and off-pump surgery. These operative differences may significantly affect long-term outcome. Absolute hospital mortality is generally higher in women, for reasons that could include decreased body size, comorbidity, emergency surgery, reoperation, low ejection fraction, hypertension, and poor diastolic function, but also general risk factor profile, including age. Satisfactory matching of the sexes in such studies is complicated by the significant preoperative differences. Recovery is more difficult in women, with higher inotropic requirements, longer hospital stay, and higher early rehospitalization. Although recurrence of angina or MI appears more frequent, fewer women are referred for repeat catheterization and/or surgery. Yet their long-term survival equals or exceeds that in men.

**Access to care**
In the past, women had fewer invasive and invasive investigations and fewer invasive interventions: a 50,000-patient survey in Ontario found that access to PCI and CABG in women post-angiography was half and two thirds that of men, respectively. However, with increasing recognition of CAD in women, these rates were evening out from 1994/1995 to 1997/1998.

**Conclusion**
We still do not know whether women are underinvestigated and undertreated or men overinvestigated and overtreated, nor whether the differences we have described are based primarily on sex or gender, ie, biology or culture (or on what combination of the two). Researchers must continue to collect the best possible evidence, and clinicians to offer diagnostics and therapy on a bias-free basis.

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Coronary heart disease (CHD) remains the leading cause of death and disability in both men and women in the industrial world. Although the misperception that CHD mainly affects men still prevails, cardiovascular disease and stroke continue to kill more women each year. It is widely known that gender differences exist not only in terms of diagnosis (anginal symptom characteristics, such as nausea, back pain, response to effort, etc), but also in the pathophysiology and management. New findings concerning the role of inflammation in the pathophysiology of atherosclerosis have revealed that the levels of inflammatory markers correlated with the risk of CHD. Two studies, the Women’s Health Study (WHS) and the Physicians’ Health Study (PHS), demonstrated that the risk of cardiovascular events was associated with the levels of inflammation markers. Interestingly, both the median levels of high-sensitivity C-reactive protein (hs-CRP) and the absolute risk in women were slightly higher than those in men in those studies. Estrogen may have a major role in the increase CRP levels. Although several trials in women taking hormone replacement therapy (HRT)—such as HERS (Heart and Estrogen-progestin Replacement Study) and ERA (Estrogen Replacement in Atherosclerosis)—showed some positive effects on lipid parameters, no reduction in risk of major cardiovascular end points and death was evidenced. Although women share many of the traditional risk factors with men, gender differences affect some risk factors. Thus, diabetes mellitus and high triglyceride levels are stronger risk factors in women than in men; women have higher levels of fibrinogen; age and menopause increase the level of homocysteine, etc. Aspirin, nitrates, β-blockers, and calcium channel blockers are widely prescribed in the management of stable angina pectoris. However, increasing age and female gender make patients less likely to be prescribed these treatments. Although there is a general underuse of antiplatelet drugs, β-blockers, and lipid-lowering medications in the treatment of stable angina pectoris, multilevel logistic regression analysis revealed that β-blockers and antiplatelet agents were more likely to be prescribed in men compared with women. Another trial emphasized the misdiagnosis and undertreatment of women with stable angina, and showed that male patients were more likely to receive aspirin and heparin, and less likely to be given cal-

Does gender influence the management of patients with stable angina?
cium channel blockers and angiotensin-converting enzyme (ACE) inhibitors, compared with female patients. The rates of narcotic and nitroglycerin administration did not differ between both genders. Use of oral anticoagulants and oral antidiabetics was more common in men, while diuretics were more frequently used in women. Most large-scale trials report the benefits of statins in the reduction of mortality, both in men and women, ie, independently of gender. ACE inhibitors were also prescribed similarly in both groups. A recent large trial, the EUROtrial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease (EUROPA), revealed no consistent benefits for both genders in the management of stable CHD when the ACE inhibitor perindopril was added to their conventional therapies. In both genders, a metabolic anti-ischemic agent, trimetazidine, was demonstrated to improve treadmill exercise parameters, and may be recommended for elderly and coronary diabetic patients, especially those with impaired left ventricular function. Women experience vaguer symptoms, which may account for underuse of effective therapies. Gender-related differences also exist in the interventional management of stable angina. Although early registries showed that women have a higher complication and mortality risk than men, in recent trials, especially in elective stenting, outcomes in women are as good as in men. Diabetes and small vessel size worsen the outcomes of both percutaneous and surgical revascularization in women. Being a woman was independently associated with a lower probability to be referred to a cardiac rehabilitation program at discharge. An age and gender bias also exists in the prescription of important secondary preventive therapies in primary care, which may lead to increased mortality from ischemic heart disease in these groups. These findings demonstrate that women who are hospitalized for CHD undergo fewer major diagnostic and therapeutic procedures than men. Physicians pursue a less aggressive management approach to coronary disease in women than in men, despite greater cardiac disability in women. In conclusion, physicians should try to focus their efforts on proper diagnosis and treatment of CHD in women because of delayed presentation and lower specificity of symptoms and diagnostic accuracy of noninvasive testing, higher complication rate, lower use of appropriate treatment and worse outcome.

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THE DISCOVERY OF THE IF CURRENT INHIBITOR PROCORALAN

Interview with J.-P. Vilaine and J.-L. Peglion

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You are the “fathers” of Procoralan, the first selective and specific IF inhibitor: what line of research did you pursue to discover this molecule?

Our research program was aimed at selecting a truly innovative compound designed for the treatment of coronary artery disease, that would be able to reduce heart rate selectively. Our starting point was based on the fact that many experimental, clinical, and epidemiological data had cast selective heart rate reduction in a very attractive light as a therapeutic mechanism in this disease.

The fundamental concept in the pathophysiology of myocardial ischemia in patients with coronary obstructive disease is that the culprit is a mismatch between myocardial oxygen demand and coronary blood flow. Under normal conditions, the heart tolerates a wide range of myocardial oxygen consumption variations. This occurs for example during exercise, where tachycardia plays a major role, through autoregulation, by ensuring a parallel increase in coronary blood flow, thereby enabling the increased metabolic requirement to be met. However, in patients with coronary artery disease, several mechanisms contribute to decreasing coronary flow reserve: fixed coronary artery stenosis, coronary vasoconstriction, and impaired vasodilator capacity of the microcirculation. In these patients, most ischemic episodes are triggered by an increase in heart rate. The decrease in coronary reserve does not allow a large enough increase in coronary flow to be produced in order to meet the metabolic stimulation caused by the increased heart rate. As a result, an imbalance between oxygen demand and supply develops, the outcome of which is myocardial ischemia.

Heart rate is the most important among the major determinants of myocardial oxygen consumption, and its increase is responsible for most ischemic episodes in patients. Heart rate reduction can prevent or reduce the mismatch between myocardial oxygen requirement and supply—which defines myocardial ischemia—by reducing myocardial oxygen consumption and by prolonging diastolic time, thus improving myocardial perfusion. Numerous epidemiological data suggest that increased heart rate is an independent predictor of mortality and that the reduction in mortality in patients with CAD or heart failure subsequent to treatment with β-blockers, some calcium channel blockers, or amiodarone results from the heart rate-lowering actions of these agents. Furthermore, experimental studies suggest that chronic heart rate reduction limits atherosclerotic lesion progression and rupture, promotes the development of coronary collaterals, improves cardiac remodeling, and has antiarrhythmic effects. These mechanisms could contribute to the improvement in CAD prognosis resulting from heart rate reduction, over and above its anti-ischemic potential. The screening of a series of benzo-cycloalkane derivatives led to the selection of Procoralan, the first selective inhibitor of the depolarizing IF current of the sinus node. In vitro, this compound reduces the spontaneous beating rate of isolated right rat atria and the action potential firing rate of rabbit sinus node preparations. This effect is explained by a decrease in the diastolic depolarization slope of the action potential and underlies the selective inhibition of the pacemaker IF current. In vivo, Procoralan induces a selective reduction in heart rate both at rest and during exercise without any change in myocardial contractility, atrioventricular conduction, and ventricular repolarization duration. Procoralan reduces exercise-induced myocardial ischemia in pigs to the same extent as a β-blocker, while eliciting a greater reduction in ischemic myocardial contractile dysfunction. The clinical development of Procoralan has confirmed its selective electrophysiological and hemodynamic effect and an efficacy equipotent to that of a β-blocker in preventing exercise-induced myocardial ischemia in patients with stable angina. Procoralan is also expected to have a beneficial effect on other clinical forms of myocardial ischemia, in particular in the presence of heart failure, as well as on the improvement of CAD prognosis.

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Keywords: Procoralan; ivabradine; heart rate; sinus node; IF current; myocardial ischemia

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The currently established drugs in the treatment of coronary artery disease that reduce heart rate, such as the \( \beta \)-adrenergic blockers and nondihydropyridine calcium channel antagonists, do not exert a selective action on heart rate. These two types of compounds reduce myocardial contractility and depress atrioventricular conduction. In addition, \( \beta \)-adrenergic blockers may indirectly modify vascular tone by unmasking \( \alpha \)-adrenergic vasoconstriction, in particular in coronary arteries, while calcium channel antagonists can induce hypotensive effects and reduce coronary artery perfusion pressure. These effects may be deleterious in the context of myocardial ischemia or may give rise to contraindications in certain patients or clinical situations.

All these reasons led us to develop a research program to identify a compound that would be able to reduce heart rate selectively by directly targeting the sinus node—the physiological pacemaker. To be specific, this meant identifying a compound able to inhibit the \( I_f \) current of the sinus node cells.

What makes the role of the \( I_f \) current in the modulation of heart rate such a pivotal one?

The fundamental mechanism underlying the spontaneous electrical activity of the pacemaker cells of the cardiac sinus node is spontaneous diastolic depolarization. During diastole, depolarization brings the membrane potential from its maximal value, at the end of the repolarization of an action potential, up to the threshold where a new action potential can develop. This phase not only generates the spontaneous activity of the sinus node, transmitted to the whole heart by the conduction system, but is also the target of the autonomic nervous system in the regulation of heart rate. The \( I_f \) current has been demonstrated to be the major current underlying this diastolic depolarization of the pacemaker cells and was shown to be directly regulated via intracellular cyclic adenosine monophosphate (cAMP), which is the second messenger of the autonomic nervous system. \( \beta \)-Adrenergic stimulation, by elevating intracellular cAMP, increases the \( I_f \) current and the slope of diastolic depolarization, thereby reducing the duration of the diastole and increasing heart rate. In contrast, vagal stimulation induces the opposite effects and reduces heart rate by increasing diastolic duration. Therefore, direct inhibition of the \( I_f \) current appears as an ideal target, as this is able to reduce heart rate not only in resting conditions, but also when heart rate is elevated, in particular when the elevation is due to an increase in sympathetic tone.

The first synthetic substance reported as being able to decrease the sinus rate at concentrations or doses much lower than those affecting other myocardial or cardiovascular functions was ST-567. Subsequently, AQA-39, a compound with a completely different chemical structure, was shown to present a similar cardiovascular profile. However, in contrast to ST-567, the reduction in cardiac frequency obtained with AQA-39 was associated with a large increase in the QT interval of the cat electrocardiogram, the mechanism of which was explained by a direct prolongation of the action potential duration, as observed in intracellular recordings from electrically driven atrial and ventricular muscle of guinea pigs. With “compound 3,” the increase in the QT interval was smaller than with AQA-39, for the same level of heart rate reduction. Finally, UL-FS 49, whose structure was very close to that of AQA-39 and “compound 3,” elicited a potent decrease in sinus rate, without concomitant negative inotropy or hypotensive effect, but still associated with an increase in action potential duration. These three compounds possess the dimethoxy phenethylamine moiety (Figure 1), which is present in a great variety of drugs, in particular those displaying a tropism for the cardiovascular system. With these three derivatives, a progressive reduction in the increase in action potential duration was achieved by modifying the aromatic moiety opposite to the phenethylamine moiety (Figure 1, upper panel).

We decided to take a different approach, and focused on modifying the phenethylamine moiety, with the aim of identifying derivatives with an enhanced selectivity for the pacemaker current versus the channels governing the duration of the action potential, so as to obtain compounds without any effect on action potential duration. To achieve this goal, it was important to design chemical structures showing a high degree of rigidity, since high rigidity often leads to high selectivity. For this purpose, we designed...
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and synthesized cyclic analogs of the phenethylamine moiety for introduction into the final structures (Figure 1, lower panel).\footnote{52}

The resulting compounds were then tested for their ability to: (i) reduce the spontaneous beating rate of rat isolated right atria; (ii) decrease the diastolic depolarization slope of the action potential of rabbit sinus node preparations, leading to a reduction in their spontaneous firing rate; and (iii) slow the heart rate in conscious rat. In addition, we evaluated the potential effect of the most promising compounds on the action potential duration of ventricular preparations (guinea-pig papillary muscle and rabbit Purkinje fibers), driven at constant frequency, to exclude compounds inducing inappropriate direct prolongation of the duration of repolarization, as had been previously shown to be the case with UL-FS 49 that could promote arrhythmias.

A number of derivatives showed a marked decrease in the slope of diastolic depolarization of the action potential of sinus node preparations, together with a very robust reduction in the cardiac rhythm of conscious rats, but their selectivity toward other channels differed markedly. Depending on the nature of the cyclic phenethylamine moiety of the compounds, different effects on action potential duration of ventricular preparations were observed: some derivatives produced a dramatic prolongation in duration; however, in contrast, S 15544, which had the most rigid cyclic phenethylamine moiety among all the compounds prepared in this project, only induced a very small increase in the action potential duration of these preparations. S 15544 is a racemic mixture of two optical isomers: we therefore subjected the camphorsulfonate salts of S 15544 to fractional recrystallization, which resolved this mixture into S 16257 (S configuration isomer) and S 16260 ($R$ configuration isomer). Both isomers were equipotent in reducing atrial rate, but S 16257 induced an even weaker effect on action potential duration than S 15544, a property not shared by S 16260, which elicited a dramatic increase in this effect. On the basis of these results, S 16257, which was later given the name Procoralan, was chosen for further pharmacological evaluation.

Once you had selected the “winner,” how did you set about evaluating its properties?

Various in vitro and in vivo experiments were used to specify the effects and mechanism of action of Procoralan.\footnote{53}

$\blacklozenge$ In isolated right atria of rat, Procoralan was shown to reduce the spontaneous beating rate in a concentration-dependent manner, with a maximal effect attained after 3 hours of application of single concentrations. Using single concentrations yielded an IC$_{50}$ of $1.9 \times 10^{-6}$ M at 3 hours (ie, the inhibitory concentration reducing the initial beating rate by 30%), in contrast to screening protocols using cumulative concentrations applied during 30 minutes, which yielded an IC$_{50}$ of $2.1 \times 10^{-6}$ M. The effect of Procoralan on beating rate was not modified in the presence of atropine, indicating that it did not act through stimulation of muscarinic receptors. A $\beta$-adrenergic blocking activity of Procoralan was excluded, since the reduction in basal rate of the preparations was maintained in the presence of increasing concentrations of isoproterenol, without any change in the 50% effective concentration (EC$_{50}$) of this agonist. In addition, binding studies indicated the absence of affinity of Procoralan for $\beta$-adrenergic and muscarinic receptors.

$\blacklozenge$ Electrophysiological studies in rabbit sinus node and ventricular preparations (guinea-pig papillary muscle and rabbit Purkinje fibers) were carried out, which confirmed the selective effect of Procoralan on the sinus node (Figure 2, page 70).\footnote{54,55}

$\blacklozenge$ In rabbit sinus node preparations, Procoralan slowed the spontaneous firing of the action potentials in a concentration-dependent manner, with a reduction of about 24% after 40 minutes of application of a concentration of $3.0 \times 10^{-6}$ M. This effect resulted exclusively from a decrease in the slope of the slow diastolic depolarization of the pacemaker cells, without change in maximal diastolic potential or in threshold potential for action potential firing. Furthermore, Procoralan did not affect the amplitude and the duration of the action potential.

$\blacklozenge$ In guinea-pig papillary muscles, Procoralan induced minimal effect on action potential duration and did not affect the other parameters.
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Figure 2. Change in action potential configuration in isolated rabbit sinoatrial node tissue (A), rabbit Purkinje fiber (B), and guinea-pig papillary muscle (C) in the presence of Procoralan $3 \times 10^{-6}$ M. Arrows show action potentials after 40 min exposure to Procoralan.

**Figure 3.** Concentration-dependent inhibition of $I_f$ current elicited by hyperpolarizing steps to $-100$ mV from a holding potential of $-30$ mV in sinoatrial node cells isolated from rabbit heart. Examples of current traces in control and after the steady-state use-dependent block of $I_f$ in the presence of increasing concentrations of Procoralan (left) and concentration-dependent curve for $I_f$ inhibition (right, $IC_{50} = 2.2 \times 10^{-6}$ M).


In rabbit Purkinje fibers, which were paced at a very low frequency, making them very sensitive to compounds that prolong action potential duration, Procoralan induced only a weak effect on repolarization duration.

At micromolar concentrations, Procoralan was found to have no depressive effect on: (i) the plateau phase of the action potential in these two latter preparations; (ii) the tension developed by the papillary muscles; (iii) the contractility of rat left atria; and (iv) the contraction of rat aorta induced with KCK (80 mM), indicating the absence of calcium channel antagonist activity of Procoralan.

The selective inhibition of the $I_f$ current underlying the effect of Procoralan on sinus node diastolic depolarization was established using the patch-clamp technique. In single pacemaker cells dissociated from rabbit sinus node preparations, Procoralan reduced the amplitude of the $I_f$ current in a concentration-dependent and use-dependent way, with an estimated $IC_{50}$ value of $2.2 \times 10^{-6}$ M (Figure 3).

On the other currents playing a role in diastolic depolarization (the outward potassium current $I_{Kr}$, delayed rectifier) and the two types of inward calcium currents, $I_{Ca,T}$ [transient] and $I_{Ca,L}$ [long-lasting]), Procoralan, at high concentration ($10^{-5}$ M), had no detectable effect on the T-type calcium current and slightly decreased the L-type calcium current ($-18.1\% \pm 0.7\%$), without significant use-dependent blockade. Procoralan also had no effect on the delayed outward potassium current $I_{Kr}$ at $3 \times 10^{-6}$ M though a slight decrease was observed at higher concentrations ($-16.3\% \pm 1.2\%$ at $10^{-5}$ M).

In vivo, the selective effect of Procoralan on heart rate was shown in different species at rest and during exercise.

In conscious rats, single administration of Procoralan, by intravenous as well as by oral route, reduced heart rate in a dose-dependent manner without affecting mean arterial blood pressure. For example, maximal reduction in heart rate was obtained 90 minutes after administration.
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Figure 4. Dose-dependent reduction in heart rate (HR) after single oral administration of Procoralan in conscious rats. Procoralan was given at 1.5 and 6 mg/kg in separate groups (n=6 per dose). Data are expressed as mean ± SEM, as percent change from predrug value. Significantly different from vehicle: *P<0.05; **P<0.01.

Figure 5. Reduction in heart rate (HR) after repeated oral administration of Procoralan (3 mg/kg/day, n=12) in conscious rats for 6 days. Data are expressed as mean ± SEM, as percent change from predrug value.

Figure 6. Dose-dependent effects of Procoralan on heart rate (HR) and QTc interval after intravenous administration in anesthetized pigs. Data are expressed as mean ± SEM, as percent change from the predrug value before the first administration.


oral administration (-11.7%±2.8% and -18.9%±2.0% at 1.5 and 6 mg/kg, respectively) and was maintained at 6 hours (Figure 4). Repeated once-daily oral administration of Procoralan was shown to selectively reduce the heart rate, measured by telemetry, once again in rats. This effect lasted 12 hours after administration and remained unchanged after administration of repeated doses (Figure 5).

* In anesthetized pigs, Procoralan, administered at increasing intravenous doses 30 minutes apart, reduced heart rate in a dose-dependent manner (from -15.7%±3.0% at 0.1 mg/kg to -36.8%±4.1% at 1 mg/kg). As anticipated from in vitro studies, Procoralan did not induce significant prolongations in the corrected QT interval of the electrocardiogram at any dose (Figure 6) and did not modify the PR interval. Furthermore, no change in arterial pressure or left ventricular contractility was observed, under these conditions.

In parallel with the lowering of heart rate, Procoralan reduced myocardial oxygen consumption, in a dose-dependent manner, without affecting the ratio of oxygen delivery to oxygen consumption, thus indicating the absence of a direct effect on coronary vascular tone.

* In normal Yucatan micropigs, the hemodynamic effects of Procoralan and propranolol were compared during treadmill exercise. It was shown that Procoralan and the β-blocker propranolol, at the same oral dose of 5 mg/kg and versus a control treatment with the vehicles, were equipotent in reducing basal heart rate and exercise-induced tachycardia. However, it was shown that only Procoralan, in contrast to propranolol, preserved the increase in contractility and cardiac output, as well as peripheral vasodilation (Figure 7, page 72). In normal dogs, the coronary and systemic hemodynamics of Procoralan (0.5 mg/kg IV) and propranolol (1 mg/kg IV) were analyzed at rest and during graded treadmill exercises in comparison with the vehicles. Both compounds induced similar decreases in resting heart rate and limitations of exercise-induced
We developed a model of regional myocardial ischemia induced by treadmill exercise in Yucatan micropigs, to mimic exercise-induced angina in patients. In this model, a fixed coronary artery stenosis of the left anterior coronary artery was achieved, which was not severe enough to induce myocardial ischemia at rest, but sufficient to limit the increase in coronary blood flow during exercise and to induce regional ischemia in the poststenotic myocardium. The animals were chronically instrumented to measure hemodynamic parameters, and ultrasonic crystals were implanted in the subendocardium to detect and quantify myocardial ischemia by measuring the shift in ST-segment of local electrocardiograms as well as myocardial contractile dysfunction (abnormal decrease from resting values in systolic segment shortening during exercise).

This model was used to compare the effects of Procoralan and propranolol, both administered orally at 5 mg/kg, as well as that of their vehicles. With this model, reproducible hemodynamic changes and regional myocardial ischemia in the poststenotic myocardium were observed under control conditions, ie, during exercise performed before any treatment, and during exercise after treatment with the vehicle only. Procoralan and propranolol were shown to be equipotent in reducing heart rate at rest and in limiting exercise-induced tachycardia (Figure 9). Neither compound modified mean arterial pressure at rest or during exercise. Propranolol significantly reduced basal myocardial contractility and its increase during exercise, whereas Procoralan did not. During exercise, in the poststenotic myocardium, both compounds reduced, to a similar extent (by 80%), the ST-segment shift on local electrocardiograms (Figure 10), but Procoralan resulted in a greater improvement in regional myocardial contractile function than propranolol. Thus, after treatment with Procoralan, the exercise-induced decrease in systolic segment shortening in the poststenotic myocardium was improved by 78% vs control exercise before treatment, whereas a significant decrease from resting values still remained during exercise after treatment with propranolol. With propranolol, the improvement in regional myocardial contractility was only 26% in comparison with control exercise before treatment (Figure 10).
What lessons does the discovery and development of Procoralan hold, and what are the prospects for the future?

The preclinical studies confirmed both the pivotal role of the \( I_f \) current in the regulation of heart rate and the selective inhibition of the \( I_f \) current with Procoralan, resulting in a reduction in basal heart rate and exercise-induced tachycardia without any modification of other electrophysiological or hemodynamic parameters. These studies also demonstrated that the pure heart rate reduction obtained with Procoralan resulted in a similar limitation of exercise-induced myocardial ischemia as with \( \beta \)-adrenergic blockers, while ensuring better preservation of regional myocardial contractility.

The clinical development of Procoralan confirmed these properties in patients, showing, in particular:

- A selective electrophysiological effect: Procoralan lowers the heart rate without modifying atrioventricular and intraventricular conduction or the QT interval of the electrocardiogram corrected for heart rate.

- A selective hemodynamic effect, in particular in patients with left ventricular dysfunction, in whom Procoralan reduces the heart rate while preserving left ventricular ejection fraction.

- The efficacy of Procoralan in preventing exercise-induced myocardial ischemia in patients with stable angina. This was demonstrated by two large-scale clinical trials, which were the first to show that selective heart rate reduction with Procoralan results in a major protection against exercise-induced myocardial ischemia at a level comparable to that afforded by the \( \beta \)-adrenergic blocker atenolol.

In future, we expect that the clinical benefit of Procoralan, at present demonstrated in patients with stable angina, will also be demonstrated in the other clinical forms of myocardial ischemia.

Procoralan could be of particular value in ischemic heart disease with left ventricular dysfunction, by preventing the deleterious hemodynamic effect of elevated heart rate, as well as the imbalance between myocardial oxygen delivery and consumption, without affecting myocardial contractility.

Regarding heart failure, the potential therapeutic value of Procoralan was recently illustrated in a rat model of ischemic heart failure, in which long-term heart rate reduction was associated with improvement in left ventricular function and structure.

However, some of the most intriguing prospects relate to the inhibition of the \( I_f \) current per se: the cardiac \( I_f \) current, which normally only occurs in pacemaker cells in the adult, has been shown to be reexpressed in ventricular cardiomyocytes isolated from human hearts explanted because of terminal ischemic heart failure. This \( I_f \) current is thought to represent an arrhythmogenic mechanism, which could benefit from the action of Procoralan.

Finally, a major challenge for the future is to determine whether, as suggested by experimental studies and mentioned above, pure long-term heart rate reduction due to \( I_f \) inhibition with Procoralan could improve the prognosis of coronary artery disease by modifying the progression of atherosclerotic lesions, the development of coronary collaterals, cardiac remodeling, and arrhythmogenic mechanisms. Again, the prospects here appear to be promising.
Le ralentissement sélectif de la fréquence cardiaque apparaît comme une approche thérapeutique attractive pour le traitement des cardiopathies ischémiques. La fréquence cardiaque représente le facteur de consommation d’oxygène myocardique le plus important et son accélération est impliquée dans la plupart des épisodes cliniques d’ischémie myocardique. La réduction de la fréquence cardiaque peut prévenir ou réduire le déséquilibre entre besoins et apports en oxygène myocardique, qui définit l’ischémie myocardique, en diminuant la consommation d’oxygène myocardique et en améliorant la perfusion myocardique par augmentation du temps de diastole. De plus, de nombreuses études épidémiologiques font apparaître que l’augmentation de la fréquence cardiaque représente un facteur indépendant prédictif de mortalité et que la réduction de mortalité dans les cardiopathies ischémiques ou l’insuffisance cardiaque observée avec les bétabloquants, certains inhibiteurs calciques ou l’amiodarone, peut être attribuée à l’effet de ces produits sur la fréquence cardiaque. Par ailleurs, des études expérimentales suggèrent que le ralentissement de la fréquence cardiaque peut limiter la progression et la rupture des lésions d’athérosclérose, favoriser le développement des collatérales coronaires, améliorer le remodelage cardiaque et avoir un effet antiarythmique. Ces mécanismes pourraient participer à l’amélioration du pronostic des cardiopathies ischémiques liée à la réduction de la fréquence cardiaque au-delà de son effet anti-ischémique. Le criblage d’une série originale de composés, de structure benzoécycloalkane, a conduit à la sélection de Procoralan, premier inhibiteur sélectif du courant dépolarisant If du nœud sinusal. In vitro, ce produit réduit, de façon directe, la fréquence des battements spontanés d’oreillettes droites isolées de rat et de déclenchement des potentiels d’action de préparations sino-auriculaires de lapin. Cet effet est lié à une diminution de la pente de dépolarisation diastolique du potentiel d’action et est sous-tendu par une inhibition sélective du courant pacemaker If du nœud sinusal. In vivo, Procoralan réduit sélectivement la fréquence cardiaque, tant au repos qu’à l’effort, sans modifier la contractilité myocardique, la conduction auriculo-ventriculaire ou la durée de repolarisation ventriculaire. Il limite de façon aussi efficace qu’un bétabloquant l’ischémie myocardique induite par l’exercice chez le porc, mais réduit mieux la dysfonction myocardique contractile qui en résulte. Le développement clinique de Procoralan a confirmé la sélectivité de son effet électrophysiologique et hémodynamique et son efficacité, équipotente à celle d’un bétabloquant, à prévenir l’ischémie myocardique d’effort chez des patients présentant un angor stable. Le bénéfice thérapeutique de Procoralan est également attendu dans les autres formes cliniques d’ischémie myocardique, en particulier avec insuffisance cardiaque, ainsi que dans l’amélioration du pronostic des cardiopathies ischémiques.
What is it like living with angina?

In many cases angina leads to a life of anxiety, depression, and fear. Many patients fear that they may die during an anginal attack and yet the symptom is often only described as a “discomfort” or “tightness” rather than pain. It is also interesting to note that many studies have shown that symptomatology is not directly related to the severity of coronary artery disease (CAD) found on angiography. People with angina also commonly believe that every attack causes damage to the heart. It is these factors that leave patients isolated and depressed, avoiding any exertion or enjoyment in life.

Data regarding the adverse impact of depression on prognosis are accumulating with studies such as that reported by Barefoot et al. In this study, 1031 patients admitted for coronary angiography were assessed for depression on admission, with a median follow-up of 15.2 years. The investigators found that surgical patients had a lower mortality than those managed medically, but that, controlling for this, the Self-Rating Depression Scale (SDS) scores were predictive of cardiac death. A total of 51.4% of the cohort with moderate-to-severe depression died of cardiovascular causes, compared with 42.4% of the mildly depressed group and 38% with no depression. Those with the most depression were found to be most at risk in the first year, showing that we need to intervene as early as possible. This is also the time to educate the cardiac patient on the benefits of lifestyle changes and increasing exercise before fears and misconceptions take hold. It is also noteworthy that the increased risk associated with depression continues after 5 years of follow-up. In this, as in other studies, the depression score at baseline was not linked to the severity of disease or recurrent events. The authors suggest that possible causes of the increased risk associated with depression are neuroendocrine function, poor compliance with medication, and increased cardiovascular risk factor profile.

Coronary artery disease (CAD) is a complex, multifactorial disease process. Angina is a common manifestation of this process, often leading to a life associated with unemployment, depression, anxiety, and social isolation. That is not to say that there are no solutions to these comorbidities and, along with the explosion of research in the pharmaceutical and technical interventions, there are many “low-tech” therapies that are effective in improving the quality of life of such patients. Imaginative, self-help programs designed for use at home are available, and refractory angina clinics have been introduced. Globally, we are beginning to acknowledge that the industrial lifestyle of inactivity, convenience food, and nicotine consumption has greatly contributed to this epidemic of atherosclerosis. Lifestyle interventions are often as challenging as the research and development, but we should not be discouraged by the enormity of the problem. Reduction in cigarette smoking has helped to reduce the incidence of the disease, and legislation, such as that passed by Ireland to ban smoking in the workplace, shows that bold initiatives can be made. Other ideas such as introducing free fruit into schools and designing buildings and housing estates that encourage more exercise are slowly working their way into public life. The paradox of CAD is that the disease is the most common cause of mortality in the West, but the remedies to help prevention are relatively simple. CAD rates have reached epidemic proportions in the more affluent parts of the world and are also increasing in urbanized parts of the developing world. The incidence of angina increases with age, so it is inevitable that there will be more people to treat as we live longer. It would also be fair to say that of all the chronic diseases afflicting the Western world, ischemic heart disease has made the most dramatic progress in treatment and prevention. This paper looks at the impact angina can have on everyday life and at some of the ways it can be ameliorated.

Keywords: stable angina; depression; lifestyle changes; rehabilitation

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Depression is a modifiable risk factor and treatment helps to improve health outcomes. Ru et al studied 1024 patients with known CAD and performed psychological as well as cardiac functional assessment. They recruited participants with previous myocardial infarction (MI), history of revascularization, and diagnosis of CAD made by a physician, and found a strong association between depression and self-reported health status outcome in all groups. Of the 1024 participants in their study, 20% had depression, and the depressive symptoms were associated with overall health status, independent of cardiac function. Participants who were depressed were in the younger age-group, had lower income, and were more likely to be female and unmarried. They were also more likely to have diabetes mellitus, to smoke, to be obese, and to have lower exercise capacity. The authors emphasize that more attention should be paid to the mental health of cardiac patients, and measures taken to treat depression.

Why does depression have an adverse effect? Does it delay presentation for treatment? A recent study by Dickens et al suggests that associated social isolation may play an important role. The authors studied people with depression before and after MI. They found that depression preceding MI was not associated with increased morbidity or mortality, but that having a close confidant halved the risk of having a subsequent cardiac event. These patients were more likely to smoke and drink heavily though these two variables were not predictive on their own. The authors postulated that people without a close confidant may delay seeking treatment for suspected MI and may be less likely to follow treatments once discharged from hospital. They also emphasized that although depression was not significantly associated with cardiac events post-MI, there was a high prevalence of depression in the sample and that it should be considered a risk factor when treating patients with CAD.

The main treatment options for depression in the coronary patient are cognitive behavioral therapy (CBT) and medication. Appels suggests that CBT would be an appropriate choice if feelings of sadness, hopelessness, and negative thoughts about the future extend beyond the diagnosis of CAD. He does point out that CBT should be offered with caution, and not offered to those in whom depression is a realistic response, ie, with a poor prognosis, rather that a distortion of the reality. Antidepressant therapy can be effective, although Appels stresses that it should be offered as part of comprehensive treatment. He postulates that many coronary patients refuse antidepressive medication for fear of being branded as having a mental health problem. Relaxation therapy using breathing techniques can be a powerful tool, especially for those reluctant to admit to, or are insensitive to, fatigue. These techniques are also useful for those patients with emotional triggers for angina. Gabbay et al studied 63 patients with CAD, and, using Holter monitoring, looked at myocardial ischemia during daily life. They found that ischemia occurred not only during strenuous activity, but also with other triggers during low levels of exertion such as anger and smoking.

Patients with stable angina form a considerable proportion of patients with CAD. They are often not included in the rehabilitation programs offered to other cardiac patients. Angina can have a deleterious impact on life, both mentally and physically. This often leads to maladaptive behavior, resulting in a sedentary lifestyle, physical deconditioning, and depression. Lewin has developed the Angina Plan, which is a cognitive behavioral self-help program. Health professionals, mainly nurses, take a distance learning course in order to deliver the program. It is designed to help alter false beliefs and anxieties and encourage healthy lifestyle changes and more enjoyment in life. This is done by reeducation, relaxation techniques, and individualized exercise programs, along with risk factor management, all supported by the health care professional. It is a practical and effective way of reaching many people in the community who may otherwise be neglected. The group in York, led by Lewin, evaluated the Angina Plan in a randomized controlled study looking at patients with newly diagnosed angina. They found that compared with usual advice and consultation given by a practice nurse, the Angina Plan significantly reduced reported angina, improved psychological well being, and increased activity levels.

Other imaginative treatment strategies have been developed. Lorig et al at Stanford University looked at 831 people suffering from at least one chronic disease and asked them to participate in an intensive 7½-week self-management program. The program was based on one used for arthritis management and was adapted for use in any of four chosen chronic diseases, one of them being heart disease. The classes included relaxation and distraction techniques, nutritional change, fatigue and sleep management, training in communication with health professionals, and the management of fear, anger, and depression. The participants were assessed at 1 and 2 years for health status, self-efficacy, and health care utilization. Those that participated in the self-management program showed a significant reduction in visits to hospital and GP and in health distress, and had increased self-efficacy. Interestingly, the improvement continued at 2 years even if some participants had more than one chronic disease with deterioration in their symptoms.

The Chronic Disease Self-Management Program developed by Lorig has been adapted for use in the UK and is part of the Expert Patient Scheme (www.expertpatients.nhs.uk). The instructors are patients, usually having one or more chronic diseases,

### Selected Abbreviations and Acronyms

- **CAD**: Cardiac artery disease
- **CHAMP**: Cardiac Hospitalization Atherosclerosis Management Program
- **EUROASPIRE II**: Second EUROpean Action on Secondary Prevention by Intervention to Reduce Events
- **MI**: Myocardial infarction
- **TENS**: Transcutaneous electrical nerve stimulation

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Living with angina: impact and treatment options – Wright

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and have attended a short training course. Similar schemes are running in Europe and Australasia.

There are many studies that illustrate the impact of behavioral change on a disease process. Ornish et al. set out to look at the short-term effects of stress management training in 46 patients with CAD and randomly assigned them to an intense intervention program for 1 month and compared them with the nonintervention group receiving conventional care. The authors addressed characteristics of many cardiac patients, including anxiety, depression, competitiveness, and impatience, by promoting behavioral changes through meditation, yoga, and relaxation techniques. The intervention group was taken to a residential, rural setting and introduced to regular programs of behavioral management as well as adhering to a strict vegan diet, avoiding sugar, salt, alcohol, and caffeine. The results showed that the treatment group, despite the fact that there was no aerobic training, improved their exercise duration by 44% on bicycle ergometry. The plasma cholesterol levels and triglycerides dropped by significant levels, and the amount of reported angina decreased from 10.1 to 1.6 per week. Left ventricular function was assessed using exercise radionuclide ventriculography and showed that in the treated group the mean ejection fraction response to exercise was significantly improved, with also some improvement in regional wall motion at peak exercise. Although this was a short-term study, it did show what can be done with relatively simple interventions. It should certainly help to inform patients that change in lifestyle can lead to dramatic improvement in health.

What other factors affect outcome?

Misinformation is widely available from friends, media, and medical staff. This can lead to unnecessary anxiety and unhelpful coping strategies. Furze et al. investigated this phenomenon using a postal survey of 132 patients and their friend or partner. The interesting finding was that the peers or partner were significantly more likely to think that people with angina should take life easy, avoid exercise, and that angina causes permanent damage to the heart. While pressure of time is often used as a reason for not discussing secondary prevention, this study shows that health professionals should use every opportunity to discuss the importance of exercise, diet, and smoking cessation.

It is sometimes thought that cardiac invalidism is caused by having overprotective support, but this is not necessarily the case. Riegal and Dracup described cardiac invalidism as low self-esteem, anxiety, and a feeling of being highly dependent on others, whatever the severity of the disease. The study comprised of 120 patients experiencing their first MI, and unaware of any preexisting coronary disease. Follow up was 1 month and 4 months post event. The significant finding was that the group of patients who perceived themselves to be overprotected recovered sooner than those who did not.

The authors observed that cardiac invalidism seems to develop when a patient's needs are not met. Neuroticism had a significantly deleterious effect on recovery and was the leading predictor of cardiac invalidism. It would appear that maximum social support should occur for about 1 month following the event with a gradual reduction over the next few months. Health care workers should look out for signs of neuroticism such as moodiness, poor concentration, surges in energy, and sluggishness.

Patient educational achievement, literacy, and socioeconomic status can also influence the prevalence of risk factors for CAD.

The likelihood of receiving appropriate treatment has been examined by a substudy of the Second EUROpean Action on Secondary Prevention by Intervention to Reduce Events (EUROASPIRE II). The investigators found that from the fifteen participating European countries, patients with known CAD and lower educational status had higher body mass index, blood pressure, glucose, and total cholesterol. In women, educational status did not affect their smoking habits, but, in men, smoking was significantly less prevalent with higher educational achievement. β-Blockers and statins were most likely to be prescribed to those with higher educational achievement, whereas those with lower educational status were more often treated with calcium antagonists and antidiabetic drugs. In order to reach disadvantaged groups in the community, including ethnic minorities, health providers should look at ease of access to their clinics, both for clinical times and transport. Outreach clinics can sometimes offer a solution.

Medication

The dramatic improvement in cardiac mortality in recent years is, in part, attributable to new medication tested with well-conducted, sufficiently powered trials. Many patients dislike taking medication, especially as the number of tablets increases. It is important to rationalize their medication list on a regular basis and explain the necessity for their prescription. Safety is often a concern mentioned by patients, but we are fortunate to have numerous studies to help support our reassurances that these drugs are safe. Some patients respond well to hearing details of such studies and their results. Regular biochemistry monitoring can help to forestall any potential harm and if adverse effects are mentioned, then a suitable alternative should be sought.

Most countries in Europe have guidelines for treating conditions such as angina. A recent EuroHeart Survey of newly presenting stable angina looked at prescribed medication of such patients. It found that 81% of patients were prescribed an antiplatelet agent, but only 48% were given a statin and 67% were prescribed a β-blocker. This shows a resistance to prescribing according to guidelines, particularly as these patients may well have to wait several months before their diagnostic tests are complete.

A group in California looked at ways of improving secondary prevention measures in patients with demonstrated CAD, prior to hospital discharge. They developed a program called CHAMP (Cardiac...
Hospitalization Atherosclerosis Management Program. The emphasis of the program was that aspirin, cholesterol-lowering medication using low-density lipoprotein (LDL) as a target, β-blocker, and angiotensin-converting enzyme (ACE)-inhibitor therapy should be prescribed unless contraindicated. The patients also received secondary prevention advice. The goal was that these medications and secondary prevention advice should be administered prior to hospital discharge, emphasizing their importance and hopefully improving compliance. The algorithm included a 6-week, 6-month, and 1-year follow-up to check fasting lipids, exercise levels, smoking status, and compliance and adjustments to medication.

Subsequently, patients in the CHAMP program were assessed and compared with non-CHAMP subjects. They found that hospital discharge rates for prescribing aspirin was 78% pre CHAMP compared with 92% post CHAMP, β-blocker from 12% to 61%, ACE inhibitors from 4% to 56%, and statins from 6% to 86%. These simple and cost-effective measures can be implemented with demonstrable results.

Fortunately, most cardiac medications are in a once-daily formula, and maybe in the future several pharmacological agents will be incorporated into one “polypill.”

How can we best help our patients?

A well-run, comprehensive rehabilitation program is invaluable. A good example is one based in Basingstoke, UK. It offers both physical and psychological evaluation so that the course will suit the patient as an individual. It also includes stress management, relaxation, risk factor modification, and an exercise program. Participants can attend for up to 6 months. The unit evaluated the outcomes of their course and also looked at the patient characteristics. Of the 1902 patients recruited, they found their course and also looked at the patient characteristics. The commonest cause for defaulting was depression, whereas age, gender, anxiety, and initial fitness did not affect compliance. Patients with a primary diagnosis of angina and those with percutaneous transluminal coronary angioplasty (PTCA) were twice as likely to default than those post MI and post coronary artery bypass grafting (CABG).

Unfortunately, those who would most benefit from cardiac rehabilitation are least likely to attend. The authors recommend that this group of patients should be identified at enrollment and particular attention given to encourage attendance.

It is important to identify cardiac patients least likely to use medical services so that they can be targeted and solutions found to improve uptake. A group of patients from the Rotherham area of North England participated in a study looking at barriers to uptake of health services. They all had stable angina and many complex reasons for not using services. There were practical issues such as poor transport and inconvenient or infrequent surgery times. The episodic nature of angina led to patients delaying consultation, along with fear, denial, a wish to self-manage, and low expectation were other reasons for poor uptake of health services. These barriers operate before general practitioners get involved, and the authors suggest that one solution would be to set up community development programs. Adherence to national guidelines helps to reduce inequality of care.

Support from health professionals is important when directing patients toward lifestyle changes. This is well illustrated in a paper looking at 6-month health outcomes of patients with angina discharged from a chest pain service. The authors followed up 57 patients admitted to hospital with chest pain and a confirmed diagnosis of CAD. Fifty-eight per cent of the participants still had angina and 72% reported shortness of breath; however, there was no rehabilitation program available for these patients, resulting in frequent contact with primary care services, which was not always appropriate or effective.

Beinhart et al looked at treatment satisfaction following admission with acute coronary syndrome and found that poor physician-patient communication and angina frequency were strongly associated with reduced satisfaction.

Although the importance of behavioral and lifestyle change is established, the provision of cardiac rehabilitation (CR) is patchy and mainly aimed at CABG patients. In the UK, it is estimated that of all the people receiving CR, 33% to 56% are post-by-pass patients, 14% to 23% are post-MI, and 6% to 10% are post-PTCA. The substantial group of patients with stable angina is truly neglected.

What about the patients refractory to interventional and pharmaceutical intervention?

It is not always possible to control angina with intervention or maximum medical therapy. The characteristics of patients with refractory angina are 3-vessel disease with well-preserved left ventricular function. They rarely suffer from arrhythmias, and cardiovascular mortality is low at 3.5% to 5% per annum, but they have debilitating angina. Some centers have set up refractory angina clinics to offer treatments using a multidisciplinary approach including cardiologists, anesthetists specializing in pain management, psychologists, and clinical nurse specialists. Although there is not much evidence to support some of the interventions, the patient should be evaluated and treated using set algorithms. Treatments such as transcutaneous electrical nerve stimulation (TENS), spinal cord stimulation, temporary or permanent sympathectomy, and enhanced external balloon counterpulsation all have their part to play in pain relief. Stem cell therapy to stimulate new blood vessel formation in the myocardium is one of the hopes for the future.

It is with risk factor modification that the most dramatic effects on mortality can be seen, as highlighted by a recent exploration of the effects of treatment and risk on CHD mortality in England and Wales. This paper shows the areas of treatment that have the most effect on mortality, namely, that ap-
proximately 40% of the reduction in mortality was attributable to the combined effects of modern cardiological treatments and almost 60% to reduction in major risk factors, particularly smoking. Of great concern, they point out that the increase in obesity, and incidence of diabetes and physical inactivity contributed to approximately 8000 additional deaths in 2000. Looking at current trends in the prevalence of these risk factors, this is likely to deteriorate in the future (Figure 1).

Conclusion
It would not be unreasonable to conclude that the incidence of angina is going to increase globally in the foreseeable future. Groups of patients most in need of attention, such as the depressed, socially deprived, and ethnic groups, need to be identified and strategies introduced to include them in all the resources available. A multidisciplinary approach is the way forward so that we inspire our patients to take control of their condition and be part of the decision making process. Angina is a devastating disease, the foundations of which are laid down prior to conception. Looking into the future, the emphasis must be on lifestyle modification or else our evolutionary journey will condemn many of us to a life of morbidity obesity leading to conditions such as CAD, a largely preventable disease.

The EU has stated that one of the objectives for the new millennium is that every child born should be free from avoidable cardiovascular disease until the age of 65. This will require enormous changes in our societies, including resisting the power of the corporate food, drink, and leisure industry. Looking at the history of our addiction to tobacco, we can see what can be achieved and we should not easily abandon the ambition to improve our quality of life no matter how enormous the task may seem.

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La maladie coronaire est un processus pathologique complexe et multifactoriel. L’angor en est sa manifestation la plus commune et ce symptôme retentit souvent sur la vie du malade, au travers du chômage, de la dépression, de l’anxiété ou encore de l’isolement social. Cela ne veut pas dire qu’il n’y a pas de solutions pour ces comorbidités et, en même temps que l’explosion de la recherche dans les interventions techniques et pharmaceutiques, sont apparus des traitements adjuvants non pharmacologiques, néanmoins capables d’améliorer la qualité de vie. Des programmes originaux qui relèvent de l’auto-assistance, conçus pour être utilisés à domicile, sont désormais disponibles et des cliniques pour l’angor réfractaire ont été créées. Globalement, nous commençons à réaliser que le mode de vie sédentaire des sociétés industrielles, le recours aux aliments tout prêts et la consommation de nicotine ont largement contribué à cette épidémie d’athérosclérose. Les interventions visant à modifier ce mode de vie constituent souvent un défi qui s’apparente à celui de la recherche et du développement, mais il ne faut pas se décourager face à l’énormité du problème. La diminution de la consommation tabagique a contribué à réduire l’incidence de la maladie et la législation, adoptée en Irlande, qui interdit de fumer sur le lieu de travail, montre que des initiatives audacieuses peuvent être prises. D’autres idées font lentement leur chemin dans le domaine public, qu’il s’agisse de la mise en place de la consommation gratuite de fruits dans les établissements scolaires ou encore de la conception d’immeubles ou de logements qui incitent à une plus grande dépense physique. Le paraadoxe de la maladie coronaire est que celle-ci représente la cause de mortalité la plus fréquente dans les pays occidentaux, alors que les remèdes destinés à sa prévention sont relativement simples. Cette affection a pris des proportions épidémiques dans la plupart des sociétés d’abondance du monde, mais sa fréquence augmente aussi dans les zones urbaines des pays en voie de développement. L’incidence de l’angor augmente avec l’âge, de sorte qu’il y aura inévitablement de plus en plus de malades à traiter dans la mesure où nous vivons plus longtemps. Il faut aussi signaler à juste titre que, de toutes les affections chroniques qui frappent les pays occidentaux, les cardiopathies ischémiques sont celles qui ont connu les progrès les plus spectaculaires en termes de prévention et de traitement. Cet article envisage l’impact que peut avoir l’angor sur la vie quotidienne et certains des moyens qui permettent de l’améliorer.
Clinical applications of exclusive heart rate reduction in emergency cardiology

by A. Díaz and J.-C. Tardif, Canada

Ivabradine is a selective and specific If channel inhibitor with proven antianginal and anti-ischemic properties, but without effects on blood pressure, systolic and diastolic function, and atroventricular (AV) node conduction. Its unique pharmacokinetic-pharmacodynamic properties, ability to selectively reduce heart rate, and lack of deleterious hemodynamic effects, result in several possible therapeutic applications for ivabradine in conditions such as acute heart failure with decreased or preserved ventricular function, shock, and inappropriate sinus tachycardia. In addition, contraindications to the use of β-blockers in patients with acute coronary syndromes represent other potential indications for ivabradine.

Pharmacological properties of ivabradine

Ivabradine (Procoralan) is a new heart rate–reducing agent that acts by inhibiting the specific If current involved in the pacemaker activity of sinoatrial (SA)-node cells. Its N-demethylated metabolite, and AV block, represent other potential indications for ivabradine. Tachycardia induced by the infusion of dobutamine or dopamine may aggravate myocardial ischemia. Ivabradine may play a crucial role in the management of these patients, limiting unnecessary tachycardia without preventing positive inotropic effects, hence improving myocardial perfusion and hemodynamic parameters in acute heart failure or cardiogenic shock. A wide range of cardiovascular emergencies may benefit from the use of ivabradine, especially in clinical situations where heart rate reduction is required, but the use of β-blockers is limited by pulmonary congestion, hypotension, or other contraindications.

Keywords: heart rate; bradycardia; cardiovascular emergency; angina; diastolic dysfunction

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S 18982, has also shown heart rate–reduction activity in animals as well as in humans. La Veille et al reported the complete profile of the pharmacokinetic properties of ivabradine. This novel agent is rapidly and well absorbed (t\text{max} = 0.75–1.5 hour) and has good bioavailability (37% to 49%). Ivabradine has extensive tissue distribution with limited protein binding. It is metabolized exclusively by cytochrome P450 3A4 to its active metabolite. The latter is eliminated by fecal and urinary pathways. The half-life of ivabradine is 2 hours, whereas that of its N-demethylated metabolite is 13 hours. In a study of healthy volunteers assessing the correlation between bradycardic activity and plasma levels of the parent compound and its metabolite, it was found that ivabradine exerts a dose-dependent heart rate–reducing effect, to which its parent compound and its metabolite contributes. In this study, the maximal reductions in heart rate during exercise were 11%±4% (10 mg) and 18%±6% (20 mg) after single oral doses (P<0.05), and 18%±4% (10 mg) and 27%±6% (20 mg) after repeated doses (P<0.01). Maximum heart rate reduction after an intravenous bolus of ivabradine was 19%±4%. The electrophysiological effects of a single intravenous administration of ivabradine were studied in patients with normal baseline electrophysiology by Camm et al. They observed that an intravenous dose of ivabradine does not prolong the corrected QT interval (QTc) or modify conductivity and refractility of the atria, atrioventricular (AV) node, His-Purkinje system, and ventricles. In addition, Manz et al studied with echocardiography the impact of a single intravenous dose of ivabradine on left ventricular (LV) function in patients with systolic dysfunction. The LV ejection fraction did not significantly decrease with ivabradine (0.2%) compared with placebo (1.7%). Other echocardiographic parameters, such as fractional shortening and stroke volume, were also unchanged after the intravenous administration of ivabradine.

Left ventricular relaxation is as crucial for optimal left ventricular function as is contractility. The negative lusitropic effect of β-blockers could therefore be potentially deleterious. Colin et al investigated the effects of ivabradine and atenolol on LV isovolumetric relaxation at rest and during treadmill exercise in chronically instrumented dogs. For a similar reduction in heart rate at rest and during exercise, ivabradine, in contrast to atenolol, did not exert any negative lusitropic effect (Figure 1, page 84).

Ivabradine has demonstrated a very good safety profile in all clinical trials to date, including the large multicenter, double-blind randomized INITIATIVE trial (INInternational TriAl on the Treatment of angina with IVabradinE versus atenolol) evaluating the antianginal and anti-ischemic effects of ivabradine versus the β-blocker atenolol in 939 patients with chronic stable angina. The most frequent adverse drug reactions have been visual symptoms, the majority being phosphenes that were transient and nonserious in nature. Importantly, the abrupt discontinuation of ivabradine has not resulted in a rebound phenomenon. Thus, these pharmacological properties of ivabradine render this drug suitable for use in cardiovascular emergencies.

**Use of ivabradine in acute congestive heart failure and cardiogenic shock**

Patients with unstable angina or acute myocardial infarction generally benefit from heart rate reduction both through a decrease in myocardial oxygen requirement and a lengthening in the duration of diastole and myocardial perfusion. However, the negative inotropic and hypotensive effects of β-blockers contraindicate their use in patients with pulmonary congestion, borderline blood pressure, overt pulmonary edema, or cardiogenic shock (defined as hypotension, poor cardiac output, and evidence of tissue hypoxia in the presence of adequate intravascular volume). LV systolic dysfunction exacerbated by β-blockade may worsen myocardial ischemia by causing pulmonary congestion and hypoxemia and by decreasing the coronary perfusion pressure gradient, the latter by reducing systemic pressure and increasing LV filling pressure. Furthermore, ischemic LV dysfunction with or without cardiogenic shock is not only characterized by systolic dysfunction, but it is also often accompanied by diastolic dysfunction. Because excessive tachycardia has deleterious consequences on diastolic function, heart rate reduction is impor-
directly on myocardial hypotension in some patients. Dopamine also acts tate inappropriate tachycardia and may exacerbate equate tissue perfusion. Dobutamine can precipi- initiates in patients with LV dysfunction and inad-

Vasoactive and inotropic agents often need to be initiated in patients with LV dysfunction and inadequate tissue perfusion. Dobutamine can precipitate inappropriate tachycardia and may exacerbate hypotension in some patients. Dopamine also acts directly on myocardial β₁-adrenergic receptors and indirectly releases norepinephrine. Tachycardia induced by the infusion of dobutamine or dopamine may aggravate myocardial ischemia. Ivabradine may play a crucial role in the management of these patients, limiting unnecessary tachycardia without preventing positive inotropic effects, hence improving myocardial perfusion and hemodynamic parameters in overt heart failure or cardiogenic shock. 

An optimal heart rate is also desirable in patients with an intra-aortic balloon pump (IABP), which is commonly used in patients with cardiogenic shock. 

Systolic and diastolic ventricular dysfunction is not only restricted to cardiogenic shock. LV function can also be abnormal in septic shock, resulting in a continuum from isolated diastolic dysfunction to combined diastolic and systolic failure. Limiting tachycardia in ischemic patients with other causes of shock is also a valuable potential application of ivabradine. 

**Acute coronary syndromes and contraindications to β-blockers** 

Although β-blockers have several side effects including depression, fatigue, sexual dysfunction, cold extremities, and gastrointestinal disturbances, in the emergency setting, bronchospasm and AV block constitute the most relevant adverse reactions that limit their use. While asthma or chronic obstructive pulmonary disease (COPD) represent only relative contraindications to β-blockade, some patients clearly develop bronchospasm and wheezing with β-blockers, which require dose reduction or abrupt withdrawal. Such patients who require heart rate reduction would clearly benefit from the lack of this side effect with ivabradine. Furthermore, some patients with both an acute coronary syndrome and COPD develop angina when treated with inhaled β-adrenergic agonists because of the resulting tachycardia. The heart rate reduction obtained with ivabradine could also very helpful in this setting. 

Patients with an acute coronary syndrome can have variable degrees of AV block that develop or are exacerbated with β-blockers. The need for selective heart rate reduction in patients with myocardial ischemia and AV-node conduction abnormalities represents another excellent indication for ivabradine. 

**Acute diastolic heart failure** 

Treatment of diastolic dysfunction to date is largely unsatisfactory. In the absence of controlled clinical trials, the management of patients with diastolic dysfunction is based on the control of factors that are known to exert important effects on ventricular filling, such as blood pressure, heart rate, and myocardial ischemia. Although epidemiological studies have suggested that 30% to 50% of heart failure patients have preserved LV systolic function, the presumption that all of these patients have isolated diastolic heart failure is probably incorrect. Nevertheless, Gandhi et al have reported a series of 38 patients with acute pulmonary edema and hypertension in whom they evaluated LV ejection fraction and regional function, both during the acute episode and 3 days after treatment. Their conclusions were similar to what many physi-
Acute heart failure and stenotic valvular disease

Another potentially valuable clinical application of ivabradine in emergency cardiology is the decompenated patient with mitral stenosis. Hydraulic laws dictate that for any given orifice size the transvalvular pressure gradient is a function of the square of the transvalvular flow rate. Thus, a doubling of flow rate quadruples the pressure gradient, and therefore situations such as stress, exercise, or tachycardia in patients with moderate or severe mitral stenosis cause a marked elevation of left atrial pressure. Tachycardia shortens diastole proportionately more than systole and reduces the time available for flow across the mitral valve. In symptomatic patients with more than a mild degree of mitral stenosis and in sinus rhythm, medication usually begins with β-blockers. The rationale for this prescription is to avoid excessive tachycardia. However, there exists some controversy about the value of β-blockers in this clinical situation. β-Blockers may decrease resting and peak exercise heart rate, but they have no beneficial effect on treadmill exercise time, aerobic capacity, and ventilatory performance. The exclusive heart rate–reducing agent ivabradine may benefit patients with mitral stenosis in sinus rhythm because of its lack of effects on blood pressure and systolic function.

The use of β-blockers is contraindicated in patients with aortic stenosis and acute heart failure. In such patients with severe aortic stenosis, angina, and pulmonary congestion, pure heart rate reduction with ivabradine may allow patient stabilization and cardiac surgery under more stable conditions.

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The intraoperative management of patients undergoing off-pump coronary artery bypass graft (off-pump CABG) surgery has distinctive and challenging features. Surgeons benefit from a “quiet” surgical field and different mechanical stabilizers are used in order to attain this important goal during off-pump CABG. During the procedure, drugs such as β-blockers, calcium-channel antagonists, adenosine, neostigmine, and edrophonium are used to produce a lower heart rate. However, the surgeon needs to manipulate the beating heart, which commonly leads to hypotension. While pharmacologically induced bradycardia is a desirable objective in order to better stabilize the target vessel, frequent hypotension episodes can preclude or limit the use of β-blockers and other agents that can also lower blood pressure during off-pump CABG. Bel et al tested different classes of bradycardic drugs in isolated buffer-perfused rabbit hearts. While nisoldipine did not interfere with LV function, the β-blocker esmolol induced marked deterioration of systolic function. Significant heart rate reduction was achieved with the pacemaker current inhibitor ivabradine, which was otherwise associated with an excellent preservation of contractility, diastolic function, and coronary flow.

Patients occasionally present inappropriate sinus tachycardia in the first few days after cardiac surgery. Once causes for appropriate sinus tachycardia, such as cardiac tamponade, have been ruled out in the postoperative setting, the use of ivabradine may allow safe heart rate reduction in relatively unstable patients or those in whom β-blockers are relatively or absolutely contraindicated.

Conclusions

Ivabradine is a selective and specific I_{1} channel inhibitor with proven antianginal and anti-ischemic properties, but without effects on blood pressure, systolic and diastolic function, and AV node conduction. It has unique pharmacokinetic-pharmacodynamic properties that allow its use in emergency settings. A wide range of cardiovascular emergencies may benefit from its use, especially in clinical situations where heart rate reduction is required, but the use of β-blockers is limited by pulmonary congestion, hypotension, or other contraindications.
LES APPLICATIONS CLINIQUES DE LA RÉDUCTION SÉLECTIVE DE LA FRÉQUENCE CARDIAQUE DANS LES URGENCES CARDIOLOGIQUES

L’ivabradine est un inhibiteur à la fois sélectif et spécifique du courant I, qui possède des propriétés anti-angineuses et anti-ischémiques bien démontrées. Elle n’exerce aucun effet sur la pression artérielle. Elle respecte, en outre, tant la fonction systolique et diastolique du ventricule gauche que la conduction auriculoventriculaire. Du fait de ses propriétés pharmacodynamiques et pharmacocinétiques uniques en leur genre, de son aptitude à réduire sélectivement la fréquence cardiaque sans entraîner le moindre effet hémodynamique délétère, les applications thérapeutiques potentielles de l’ivabradine sont nombreuses, dans des situations diverses telles l’insuffisance cardiaque aiguë avec ou sans altération de la fonction ventriculaire, le choc ou encore la tachycardie sinuseuse inappropriée. Chez les malades atteints d’un angor instable ou d’un infarctus du myocarde à la phase aiguë, la réduction de la fréquence cardiaque est en général bénéfique, car elle permet à la fois de diminuer les besoins en oxygène du myocarde et d’allonger la durée de la diastole autant que celle de la perfusion myocardique. Cependant, du fait de leur effet hypotenseur et de leur effet inotrope négatif, les bétabloquants sont contre-indiqués face à un tableau de congestion pulmonaire, d’hypotension artérielle ou encore de choc cardiogénique. L’ivabradine, pour sa part, n’exerce aucun effet significatif sur la fonction systolique ou diastolique du ventricule gauche ou sur la pression artérielle ; cette molécule est donc appelée à jouer un rôle privilégié dans le contrôle de la fréquence cardiaque dans ces situations cliniques hémodynamiquement instables. En outre, d’autres contre-indications aux bétabloquants chez les malades atteints d’un syndrome coronarien aigu, telles un bronchospasme ou un bloc auriculoventriculaire représentent des indications potentielles pour l’ivabradine. La tachycardie in-duité par la perfusion de dobutamine ou de dopamine peut ag-graver l’ischémie myocardique et, dans ce cas de figure, l’ivabradine peut jouer un rôle crucial en limitant l’augmentation inutile de la fréquence cardiaque sans pour autant s’opposer aux effets inotropes positifs de ces médicaments, ce qui permet d’améliorer à la fois la perfusion myocardique et les paramètres hémodynamiques aussi bien dans l’insuffisance cardiaque aiguë que dans le choc cardiogénique. Des urgences cardiologicals variées peuvent bénéficier de l’apport de l’ivabradine, tout particulièrement quand elles surviennent dans des situations cliniques où la réduction de la fréquence cardiaque est requise, alors que le recours aux bétabloquants est limité par l’existence d’une congestion pulmonaire, d’une hypotension artérielle ou d’autres contre-indications.
Jean-Baptiste Baillière (1797-1885)
The pioneering publisher who promoted French medicine throughout the world

by C. Régnier, France

Jean-Baptiste Baillière (1797-1885) was no ordinary publisher. His bookshop business was marked by its longevity: J.-B. Baillière lived 88 years and was a publisher for 67 of them. Then his brothers, nephews, sons, and descendents continued to run the family business. Even if today there is no longer any family link with the founder, the firm of J.-B. Baillière still exists, and the present company continues to publish the highly respected La Revue du Praticien and Les Archives des Maladies du Cœur et des Vaisseaux.

However, the real claim to fame of J.-B. Baillière was the quality of the works he published. J.-B. Baillière employed the best printers and the most skilled engravers and lithographers. He was one of the pioneers of the publication of photographic illustrations. But even more important than the technical quality of his publications, J.-B. Baillière’s reputation was in large part due to the eminence of the authors selected. The great names of French medicine in the 19th century were published by J.-B. Baillière. Intransigent concerning deadlines for reception of manuscripts, stingy with the number of authors’ copies, the publisher was both feared and respected. This didn’t keep him from making friends for life, notably with Claude Bernard, Émile Littré, Charles Daremberg, and Jean-Baptiste Bouillaud.

Jean-Baptiste Baillière survived three monarchies, two empires, three revolutions, and two republics. Steering clear of political convulsions, he was and remained both a bookseller in Paris and publisher of medical and scientific books and journals. He devoted his life to this one aim, and swept along in his wake sons, brothers, nephews, and grandsons. The success of J.-B. Baillière was not only that of a shrewd and groundbreaking businessman, but also of an outstanding professional publisher who contributed to the creation of the Paris Booksellers Society, the international regulation of author copyright protection, and the organization of the profession of publisher in France. Inspired by the excellence of French medicine at the start of the 19th century, driven by a romantic ideal of the exchange of knowledge between peoples, he developed a vast network of representatives and family branches throughout the world. Baillière family members made their homes in England, the Americas, Australia, Spain, and elsewhere. But, J.-B. Baillière was above all the publisher of the greatest names in French medicine: Claude Bernard, Bichat, Bouillaud, Cabanis, Cruveilhier, Daremberg, Davaine, Dupuytren, Esquirol, Flourens, Grisolle, Guyon, Huchard, Laennec, Laveran, Littré, Louis, Magendie, Malpighi, Nélaton, Portal, Rayet, Ricord, Trouseau, Velpeau, Vidal, and Villemin. The worldwide reputation of the Baillière publishing house endures to this day with such flagship medical journals as La Revue du Praticien and Les Archives des Maladies du Cœur et des Vaisseaux.
Last but not least, perhaps the most original aspect of the Baillière publishing house was its early interest in internationalization. Aided by the then unsurpassed reputation of French medicine, and particularly that of the Paris School at the beginning of the 19th century, J.-B. Baillière rapidly distributed his authors’ works throughout the world. Members of the family departed to England, America, Australia, and Spain in order to become publishers themselves.

The golden legend of Jean-Baptiste Baillière

The fourth son of ten children, J.-B. Baillière was born in 1797 in Beauvais where his grandfather and father were master drapers. The family business collapsed after the closing of the Beauvais tapestries and after Napoleon had imposed a blockade against British goods. The young Jean-Baptiste, aged 15, was sent to Paris where he arrived on June 3, 1812. One of his cousins introduced him to the Méquignons, distant relations of the Baillière family, who had a bookshop in the rue de l’École de Médecine at the heart of the what had, ever since the Middle Ages, been the university sector, the Quartier Latin. Hardworking, lively, and very talented, the Méquignon’s new assistant classified books, helped at the auctioning of old books, and rapidly learned the tricks of the bookseller’s trade.

This was a major asset. All his life J.-B. Baillière was admired for his perfect understanding of the “market” for old books, and for his ability to catalog collections of works on biology and medicine bought when bookshops or medical libraries (like that of Dr François Broussais) were sold. Physicians of the first half of the 19th century relied to a great extent on the writings and anatomicoclinical observations of the authors of the previous century. The fact that J.-B. Baillière was indeed a shrewd connoisseur of books is confirmed by the catalog of his personal library.1-3

In 1818, just six years after his arrival in Paris, J.-B. Baillière opened a small bookshop at 14 rue de l’École de Médecine, a neighborhood where such shops proliferated; indeed, his own shop moved around the same street several times. In 1819, he met Dr Félix Séverin Ratier (1797-1866) who had translated the 1st-century Roman physician Celsus. Eventually, he married his sister (unfortunately, she was to suffer an early death, in 1827). This connection gave him entry to the Paris medical circle.4 Not yet having his publisher’s certificate, Baillière published theses and bought collections of books. He obtained the requisite publisher’s certificate (n°1625, dated July 12, 1821), and thus the right to publish. He rapidly launched his first work Essays on the Physical Education of Children written by his brother-in-law, Doctor Ratier. In 1824, the Baillière catalog already boasted forty titles. Publishing success arrived rapidly with the printing of New Elements in Medico-Surgical Pathology or the Precise Theory and Practice of Medicine and Surgery by Louis Charles Roche (1790-1895) and the elder Joseph Sanson (1790-1841), respectively students of Joseph François Broussais (1772-1838) and Guillaume Dupuytren (1777-1835). The work was republished four times in 25 years, and was a mainstay of medical teaching in France. Despite the serious competition of editors of medical dictionaries like Panckoucke or Béchet, the Baillière publishing house published (or copublished) the Dictionary of Practical Medicine and Surgery (1829), compiled by medical leading lights and dubbed “the fifteen volumes.” It was this dictionary that truly launched the reputation of the House of Baillière. Forty-seven years after the 1st edition, Sigismond Jaccoud was given the task of completely revising the dictionary, which became the New Dictionary of Practical Medicine and Surgery. However, it was not quite as successful as the hundred-volume dictionary of Amédée Dechambre published between 1864 and 1869 by Victor Masson. There was also the no less celebrated Dictionary of Medicine, Surgery, Pharmacy, Minor Sciences, and Veterinary Art, with a complex publishing history. The first 8 editions were published by Brosson, then Brosson and Chaudé, then Chaudé. In 1845, the rights were acquired by J.-B. Baillière for the 9th edition. The editorial history is even more complex. The first edition, compiled in 1806 by Joseph Capuron, was followed by a second edition in 1810 by the same and Pierre-Hubert Nysten. Nysten then compiled the successive editions, initially single-handedly, then with Émile Littré. In 1855, Émile Littré prepared an entirely revised version, and was in charge of all successive editions until the 21st and final edition in 1908.1,4,5
The social and professional progress of J.-B. Baillière seemed ineluctably placed under the sign of success despite the death of his wife on January 19, 1827. This same year, he became “publisher to the Royal (then Imperial) Academy of Medicine,” and held the post until December 1871, when Baillière was “dismissed” and replaced by Masson.

To ensure he remained in the headlines and to safeguard his reputation, he published (at a loss) the *Annals* and the *Bulletin* of the Academy. He then began publishing specialized medical journals and reviews including the *General Archives of Medicine* (1823-1856), the *Weekly Journal of Medicine* (1828-1830), the *Annals of Public Hygiene and Legal Medicine* (1829-1856), the *Journal of Medico-Surgical Knowledge* (1833-1856), and *The Experience* (1837-1844). These publications enjoyed a relatively large circulation, but curiously Baillière did not know how to exploit this kind of journal and he was left behind by his eternal rival Victor Masson. Yet, these journals had the advantage of covering the whole field of medical knowledge and were a good hunting ground for promising young talent.

In 1828, after one year of being a widower, J.-B. Baillière married Marie-Georgette Meaux Saint-Marc (1808-1859), the daughter of a rich businessman, shareholder of the Bank of France.

In 1847, J.-B. Baillière was elected vice-president of the Booksellers Society, alongside Ambroise Firmin Didot (1790-1876), Louis Hachette (1800-1864), and Victor Masson (1807-1879), three great names of French publishing. Three years later, thanks to the support of his father-in-law, he occupied one of the twelve seats of the very powerful Discount Committee of the Bank of France, thus marking the entry of capitalistic publishing into the economic life of France. In 1864, invoking reasons of health (poor eyesight) he abandoned his seat to his eldest son Émile.

On the death of J.-B. Baillière, on November 8, 1885, his sons Émile (1831-1920) and Henri (1840-1905) inherited the business. Émile had become a partner in 1856 and Henri in 1871. In his will of 28 March 1885, their father had written: “I leave a fortune much greater than I could ever have hoped, this is neither due to luck nor speculation. I owe it to my persevering work, to the intelligent and devoted support of my wife, to order, to economy, to sound investments, and to the increase in the value of money. The “sound investments” mainly concerned the purchase of 364 hectares of rich agricultural land in Brie and to investments in various Paris properties, including the historic J.-B. Baillière and Sons building, 19 rue Hautefeuille, Paris 6.

In the Baillière family, Jean-Baptiste had not been the only one to launch himself into medical publishing and succeed. In 1829, his younger brother, Germer Jules (1837-1905), inherited the estate of Mme Auger-Méquignon and opened his own publishing business. On the death of his father, Gustave-Germer (1837-1905), he took over the business and then in 1875 became an associate of Félix Alcan (1841-1935), who continued alone after 1883.
An intransigent publisher

On Sunday June 15, 1862, in his vast property of Bonfruit near Melun (South-East of Paris), J.-B. Baillière, then aged 65, had invited several important guests to celebrate his fifty years as publisher. Among them were Claude Bernard (1813-1878), the founder of experimental medicine; Jean-Baptiste Bouillaud (1796-1881), who had been Balzac’s doctor and the first to describe acute articular rheumatism, which was to be named after him (maladie de Bouillaud); Charles Daremberg (1817-1872), who had interpreted the texts of Galen; Émile Littré (1801-1888), translator of the works of Hippocrates; and Count de Germiny (1799-1871), governor of the Bank of France. Also invited was Louis Hachette, who addressed the guests and declared J.-B. Baillière to be “an intelligent and perspicacious editor and publisher, who had detected and encouraged the talents of a considerable number of young students who later became an honor to the medical intelligentsia.” His son-in-law, the psychologist Auguste Félix Voisin (1829-1898), added, “our friend has given disinterested and generous help in various circumstances to young doctors who today practice with distinction in our capital, and who, demoralized and exhausted by misfortune at the start of their career would never have overcome the obstacles without his help.”

Having a prodigious memory—as he himself claimed—J.-B. Baillière had a reputation for reliability, for the rapidity of his work, for the rigor of his corrections, for the quality of his suppliers (paper makers, printers, lithographers), and he always selected his engravers himself. On June 14, 1829 he wrote to Isidore Geoffroy Saint-Hilaire (1805-1861), several months before the publication of the author’s Treatise on Teratology. “As far as the execution of drawings and lithographs is concerned, you can be sure I attach as much importance to it as you. The draftsman will be the one you yourself have chosen, our Mr Martin.”

The catalog of the personal library of J.-B. Baillière contains a great number of works dealing with publishing, as well as essays on engraving and the techniques of printing. However, the character of the editor sometimes appears to have been rather brusque—a letter written by Jean Cruveilhier on August 17, 1828 suggests this: “The Sunday you have spent with me has completely dispelled the unpleasant impression that your earlier brusque manner and immoderate expression made.”

Letters between authors and J.-B. Baillière show that the editor sometimes obtained for them books and articles they themselves could not find (thanks to his network of correspondents in France and abroad)—thus remaining faithful to his trade of bookseller. On October 16, 1824, the zoologist and paleontologist Gérard Paul Deshayes (1795-1875) wrote to J.-B. Baillière: “You would do me a great service if, while browsing through books, you could find me for 20 or 25 francs (it’s expensive) a book entitled On the Oryctology of the Region Surrounding Brussels, by Bertin.” (“Oryctology” is an old name for mineralogy, geology, and paleontology all in one.) Similarly, in a letter to J.-B. Baillière dated September 3, 1866, Paul Bert (1833-1886) wrote: “I would like to know where the work by Haidenhain on the transformation of movement into animal heat was published. Perhaps in the journal of Duboys-Reymond or in his archives? The date must be around 1865 or 1866.”
J.-B. Baillière was uncompromising concerning deadlines: the letters written by authors presenting their apologies for being late illustrate their apprehension. In a letter dated September 18, 1832, at the time he was compiling his vast *Pathological Anatomy of the Human Body*, Jean Cruveilhier tried to play for time: “Your reproaches are perfectly justified, my dear Mr Baillière, I will give you top priority until I have finished the 13th, 14th, and 15th deliveries. Please be patient and all will be well.” The same apprehension is echoed by the surgeon Joseph François Malgaïne (1806-1865) who on November 20, 1837 wrote to J.-B. Baillière: “You sent me a preposterous letter, but I will gladly let it pass since this delay must be as exasperating for you as it is for me (…) Your printers must be practical jokers” If manuscripts were long overdue, the financial penalties were pitiless, as Isidore Geoffroy Saint-Hilaire found to his cost in 1836 when volumes II and III of his *Treatise on Teratology* were published. The son of the famous naturalist had delivered the manuscripts three years late. He wrote to J.-B. Baillière: “I was astonished to read your demand that I forgo my rather scanty fees of 1500 francs for the treatise, and I am sure you would not have suggested it if you had had before your eyes copies of your letters in which you offered me 2400 francs in 1833. My legal right now would be to make drastic cuts in the manuscript.” Other authors tried to strike the right chord, like the famous neurologist Charles Édouard Brown-Séquard (1817-1894) who wrote on May 19, 1856: “I am convinced that you and I have much to gain thanks to the delay in my delivering the manuscript to you. As you know I have recently been awarded the prize for experimental physiology and, moreover, all the principal journals in Europe and the United States have taken an interest in my work and have given me high praise. Thanks to this… the sales of my book will be increased considerably.”

**The international penetration of French medicine through the Baillière network**

Since he planned to translate French medical texts and distribute them abroad himself, J.-B. Baillière decided that his company had to be international. Fearing that the books in his catalog would be pirated, he was an ardent defender of literary copyright. His international expansion was greatly assisted by the prestige that French science enjoyed in the 19th century. On the first of June 1826, on the occasion of the opening of his branch in London, he published a paragraph in English: “Thanks to the present period of peace, the advantage of facilities for communication between the nations favors the establishment of a regular correspondence between the men of science and the rapid transmission of discoveries from one people to another.” J.-B. Baillière called upon the services of his family, and sent his youngest brother to England and a nephew to Spain; his sons departed to study the book-selling business in Germany. On arrival in a new country (England, Spain, United States, Australia), the Baillières exhibited an extraordinary “faculty of integration”; in less than one generation they had become English, Spanish, American, or Australian. Their father also established a very dense network of correspondents, which enabled him to do without agents.

**A planned family dispersion**

In the first half of the 19th century, J.-B. Baillière busied himself with the editorial conquest of the English- and Spanish-speaking world. It was much easier to penetrate these countries than the Germanic ones, who had a strong editorial tradition. In the German-speaking regions he relied instead on correspondents.

In 1826, J.-B. Baillière opened a branch in London under the direction of his brother Hippolyte (1809-1867). On the first of June, the two brothers published an announcement, a sort of profession of faith in which they undertook to sell the journals printed in France at the same price in London as in Paris, at an
J.-B. Baillière and the First Stirrings of Medical Photography

On January 17, 1839, François Arago (1786-1853) addressed his colleagues of the Academy of Science: “M. Daguerre has developed special plates on which optical images leave a perfect print where everything that the image contains is reproduced down to the most minute detail with an exactitude and a sharpness that are incredible.” This date has gone down in history as the official birth of photography. The idea of using photographs in medical books took root quite rapidly in the minds of publishers, and J.-B. Baillière was to play a pioneering role thanks to three reference books:

◆ An atlas, Courses in Microscopy Complementary to Medical Studies, by Alfred Donné and Léon Foucault, published by J.-B. Baillière in 1845 (75 pages).18
◆ The celebrated Album of Pathological Photographs a companion volume to Localized Electric Shocks, by Guillaume Duchenne de Boulogne, published in 1862 (40 pages).19
◆ Photographic Iconography of the Nerve Centers (1873) by Jules Bernard Luys, consisting of a book (114 pages) and an atlas (135 pages).20

◆ Microbiology
Microscopic objects were among the first to be photographed. The technique was difficult because of problems of lighting and the lack of contrast in microscopic objects; moreover, the question of optical convergence between the microscope and the camera obscura had not been resolved. On February 24, 1840, the hematologist Alfred Donné (1801-1878) presented to the Academy of Science photomicrographs taken with a solar microscope (he had replaced the eyepiece of his microscope with a plate). Donné and his assistant, the physician Léon Foucault (1819-1868), had succeeding in fixing images of bone tissue, dental tissue, and some natural samples on daguerreotypes. For six years, the two men carried on their photomicrographic studies and solved the problem of lighting by replacing sunlight (variable and thus often insufficient) with artificial light obtained by the combustion of hydrogen in oxygen in the presence of lime. In 1844-1845, Baillière published Donné’s Courses in Microscopy, which was accompanied by an 45 x 32.5-cm atlas with 20 plates each illustrated with four images produced using the daguerreotype method (magnification × 200 or × 400). It was one of the first medical books illustrated with engravings inspired by daguerreotypes. In it Donné described “globulins,” later called platelets, for the first time, as well as Trichomonas vaginalis. Donné paid homage to J.-B. Baillière: “because our editor showed so much good will and desire to make our work as perfect as possible, we did not hesitate to multiply the plates and show several when one might well have been sufficient.”18

◆ The physiology of movement
The advent of photography made it possible to compensate for the shortcomings of the human eye, which was incapable of grasping the separate instants of a displacement or a movement. In 1852, Doctor Guillaume Amand Duchenne (known as Duchenne de Boulogne) (1806-1875) and Adrien Tournachon (the brother of Félix Tournachon, aka Nadar, the celebrated photograph) (1825-1903), began a series of studies on human physiognomy. Duchenne photographed his patients undergoing “electrophysiological stimulation” and wrote: “using electrophysiological analysis and with the aid of photography, I will demonstrate how to paint correctly the expressive lines of the human face, which one might call the orthography of the physiognomy of movement.” Electrodes placed on the face induced a contraction of the muscles involved in the principal expressions of the human face (the “passions”). In 1862, Duchenne entrusted J.-B. Baillière and the widow of Jules Renouard with the publication of his famous treatise: The Mechanism of the Human Physiognomy, or the Electrophysiological Analysis of the Expression of Passions that are Relevant to the Practice of Plastic Arts. It was illustrated with 74 portraits on albumen paper. Duchenne also photographed patients with neurological disorders and published sixteen of the images in his Album of Pathological Photographs (22.5 x 29 cm) published in 1862 by Baillière. This book was one of the first works in France to use albumen photographs of clinical cases (11 x 18 cm).19

◆ Neuroanatomy
The neuroanatomist Jules Bernard Luys (1828-1897) is famous for his description of the accessory band of the superior olive nucleus and the centromedian nucleus to which he has given his name (centre médian de Luys). His Photographic Iconography of the Nerve Centers published in 1873 by J.-B. Baillière and Sons consisted of an 27 x 35.5-cm atlas with 70 photographs on albumen paper; the images were of different sizes and were glued on the right-hand page while on the left-hand page a lithograph gave the numbers of the titles (which could be consulted in another volume). To obtain good prints, Luys always took care not to use chromic acid in his anatomical preparations, since on hardening it gave a greenish color to the preparations and had the disadvantage of being refractory to light. His youngest son, Georges Luys (1870-1953), a doctor, also took numerous photographs. The father justified his illustrations of anatomical observations “because I wanted to be understood at any cost.” In 1883, he published, again with J.-B. Baillière, Research on the Structure of the Brain Membrane Using the Microphotographic Method, which also contained photographs on albumen paper.20

Photographic plate of brain section, from the Iconographie Photographique des Centres Nerveux – Atlas [Iconography of the Nerve Centers- Atlas] by Jules Bernard Luys, published by Baillière in 1873. Baillière was among the first medical publishers to use photography. Photo courtesy of BIUM (Bibliothèque Inter-Universitaire de Médecine), Paris.
exchange rate of one franc for one shilling. Thus, all new publications and journals in all branches of medicine and science would be available in London within 15 days of their appearance in Paris. In April 1830, the Baillière bookshop published its first catalog of books, which consisted not only of French and German translations, but also original works by English physicians and botanists; success was complete when the bookshop was accredited by the British Museum. Having moved to 219 Regent Street in 1831, the bookshop was financially independent of the parent company in Paris. The success of the London Baillière branch very rapidly inspired emulators in the family, and three Hippolyte sons emigrated to the United States and Australia. In 1869, two years after the death of her husband, Madame Hippolyte Baillière sold the London business rights to two English editors, Albert Alfred Tindall (1840–1931) and George Cox (1828–1899); the Baillière bookshop became the Baillière, Tindall, and Cox Publishing House, known to all British doctors.

In 1848, in Madrid, Jean-Baptiste’s nephew Charles François Bailly (1825–1909), known as Carlos Bailly-Baillière, translated and edited French authors for the Spanish-speaking medical students. Carlos even founded a printing works. The Bailly-Baillière books were exported to the Spanish colonies of South America. His sons Antonio (1866–1909) and Enrique Bailly (1864–?) took over the bookshop, which finally disappeared in the torments of the Spanish civil war in 1936.

Around 1855, J.-B. Baillière sent his eldest son, Émile (1831–1920) aged 20, to Leipzig, the metropolis of the book trade, to learn his craft and to study German printing techniques. Apprenticed to Weigel, Émile acquired a good knowledge of the industrial organization of bookshops in Germany, and retained close links with the publishing houses in Leipzig. J.-B. Baillière was the French translator and editor of Cellularpathologie (Cellular Pathology, one of the founding texts of modern medicine) of Rudolf Virchow (1821–1902), who himself supervised the quality of the translation.

In 1851, Pierre-François Hippolyte Baillière (nicknamed “the Englishman”) sent his sons Hippolyte Émile (1832–1920) and Charles Edmund (1834–?) to the United States; the first became a paper manufacturer in Newark, New Jersey, before opening a bookstore. He then founded, with his brother Charles Edmund, the Baillière-Brothers Company in New York, which published books on Broadway from 1851 to 1868. In 1860, Ferdinand François (1838–1881), another son of Pierre François Hippolyte, opened a Baillière bookstore in Melbourne (Australia). Three years after his arrival he was official editor to the government of the state of Victoria. He made friends with Doctor George Beaney (1828–1891), surgeon general of Melbourne Hospital, and published medical books and the first Australian medical journals: The Medical and Surgical Review (1863), The Australian Medical Journal, and The Melbourne Medical Record (1873). Because of its small population, the British colony did not have enough doctors to keep an editor busy, so Ferdinand François Baillière also published nonmedical books. Thus, in 1875, Baillière published a book with photographs of the pictures in the Melbourne National Gallery. This work is important in the context of 19th-century Melbourne publishing and equally important in the context of Baillière’s work. It is one of the earliest catalogs to feature pictorial aspects of an Australian gallery collection. Diversifying even further, Ferdinand François Baillière also bought and sold surgical instruments, scientific material, microscopes, and skeletons.
In 1862, after having completed his law studies, Henri Baillière (1840-1905), the second son of J.-B. Baillière, went to Germany to make professional contacts in Berlin. He traveled throughout Egypt in 1867 and wrote a book on his impressions of the country.\textsuperscript{16}

The Baillière network throughout the world
Apart from the four branches he established in England, the United States, Australia, and Spain, which published and sold books (both medical and nonmedical) in English and Spanish, J.-B. Baillière set up a network of correspondents throughout the world who ensured the sale of his books. These correspondents not only distributed the French authors published by J.-B. Baillière, they also served as “scouts” and proposed to the Paris publisher works by famous authors published in their own country that they would edit and translate into French themselves. The correspondents were also much solicited by J.-B. Baillière when seeking rare editions or books not available in France for his own authors.

The names and locations of retail bookshops in the Baillière network mentioned on page 2 of the Nysten Dictionary of Medicine (1858 edition) were those of 107 bookshops of which 53 were in France and 54 in 12 other countries. This internationalization reflects the worldwide respect for French medicine in the middle of the 19th century. There were 16 correspondents in Italy, 10 in Belgium, 7 in Russia, 6 in Holland, 5 in Germany, 3 in Portugal, 2 in Sweden, and one each in Havana, Mexico, Warsaw, Geneva, and Athens.\textsuperscript{17}

In 1910, the House of J.-B. Baillière and Sons could claim to have more than 800 correspondents distributed throughout the world.\textsuperscript{12}

Baillière today
J.-B. Baillière long resisted the urge to publish medical journals. And yet, ironically, it is through a journal that the link has been preserved between yesterday’s family-run enterprise headed by five generations of Baillières—an enterprise that weathered such momentous events as the Industrial Revolution and several major wars, including World War I and II, during the 19th and 20th centuries—and today’s incorporated company. This journal is the famed La Revue du Praticien—an obligatory read for all French physicians even today—which was started in 1951 by Dr André Roux-Dessarps–Baillière, and which continued under his son Gérard (also a doctor), in collaboration with his nephew, Henri Morel d’Arleux-
Jean-Baptiste Baillière (1797-1885): pioneering publisher – Régnier

Bailière. Unfortunately, the family was plagued by recurrent health problems that prevented them from carrying on their publishing activities. By a quirk of fate, and faithful to the long-established Bailière tradition of internationalization, the publishing house once again, in 1987, moved across the Channel to London and came into British ownership... only to return to its French roots, in 1999, in Paris, under the name Groupe JB Bailière Santé.

Publication of La Revue du Praticien continues to this day, with three different editions: the standard edition of La Revue du Praticien destined for all physicians (indexed in the MEDLINE database and hence accessible to all doctors throughout the world), and its two offshoots, La Revue du Praticien – Médecine Générale, started in 1987, to reflect the newly created specialty of general medicine, and La Revue du Praticien Gynécologie et Obstétrique, started in 1988, for gynecologists, obstetricians, midwives, etc. Another leading publication, Les Archives des Maladies du Cœur et des Vaisseaux, was also created in 1908, and is indexed in MEDLINE. Bailière is well known for the numerous, well-attended symposia and congresses it organizes, and has developed several web sites to increase its reach to French-speaking doctors and provide a wider international basis for its publications.

This article is based on family archives selected by Mr Michel Roux-Dessarps.

REFERENCES
10. Private and family collections of autographs and correspondences between Jean-Baptiste Bailière and his authors.
12. Family archives of Mrs Gérard Roux-Dessarps and Mr Michel Roux-Dessarps.
Jean-Baptiste Baillière (1797-1885): l’éditeur visionnaire qui diffusa la médecine française à travers le monde

The French broadsheet press in the 1830s was a saturated market that forced editors to come up with new solutions if they were to publish and survive. Émile de Girardin’s *La Presse* (1836) maintained the format of the traditional political newspaper, but halved the subscription rates. Three years earlier, *Le Magasin Pittoresque* had offered what it termed “useful” knowledge, accompanied by woodcuts. Its editor-in-chief for nine years, Édouard Charton, then visited London in the summer of 1842 and discovered a new type of illustrated paper, *The Illustrated London News*. This weekly broadsheet had thrown its news pages open to images, contending that these were more readable, and above all a better reflection of reality. On returning to Paris, Charton propounded this approach to two journalist-publishers, Jean-Baptiste Paulin and Jean-Jacques Dubochet, who were already well-known for having produced *Gil Blas* (1835) and *Don Quichotte* (1836) in illustrated editions sold in weekly installments—a system that not only provided publishers with ready cash, but also groomed a readership network avid for illustrated texts.

The Illustrated news press that came into being almost simultaneously across mid-19th century Europe was little less than a revolution. Periodicals such as Charivari in France were already renowned for their satirical prints, but the mid-century saw the press putting topical images to more attractive and didactic use, led by series of weeklies. In the vanguard was the *Illustrated London News* (Britain, 1842), which appears to this day, followed by *L’Illustration* (France, 1843-1944), the *Illustrierte Zeitung* (Leipzig, 1843-1940), and a host of other illustrated periodicals worldwide in the 1860s. Editorial offices fed the boom by employing teams of draftsmen and engravers, soon joined by photographers. *L’Illustration*, founded by Édouard Charton, Jean-Baptiste Paulin, and Alexandre Dubochet, was an instant success, attracting tens of thousands of loyal readers with its high-quality prints, wealth of news items, contributions from a network of correspondents, and an ever-increasing reliance on images. Prints were created mainly from drawings, but *L’Illustration* lost no time in using photographs, beginning in 1848—even if, in those first decades, they required an engraver’s input before they could be published (half-tone mechanical reproduction came only in the 1890s). The paper offers a panorama of sociopolitical, scientific, and cultural life in the 19th century. Issues were devourd by their contemporary readership and have since become collectors’ items in book fairs and flea markets. *L’Illustration* was a key player in the history of the French press and a founding member of modern media-driven society.

*Imaging the world: L’Illustration: the birth of the French illustrated press and the introduction of photojournalism in the mid-19th century* by T. Gervais, France

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Creation of an illustrated newspaper

*L’Illustration* was founded in 1843, with Dubochet et Paulin injecting a sum of 375,000 francs (of that time), or 150 shares at 2500 francs each. Fifty other shares were issued, bringing the total capital to 500,000 francs. For having come up with the basic idea, Charton was given two shares which he sold for 60,000 francs in the fall of 1844. This represented an appreciation of 1200% over 18 months, and was a resounding confirmation of success. It underlines the message that between 1836 and 1844, images had begun to pay and were attracting investors accordingly.

The first issue of *L’Illustration* appeared on Saturday, March 5, 1843. Despite the editors’ denial of political partisanship, the “History of the Week” section, the choice of cultural articles, and the way they were handled all expressed, in the view of a modern historian, “the desire to maintain the status quo, even if this was not always conscious.” Many reports dealt with railroad construction, printing works, telegraphy, and photography, reflecting an era of innovation and technical progress. Travel stories from inside France, the United States, and above all the new colony of Algeria conveyed a message of advancing Western civilization. Book, theater, and art reviews echoed the annual Salons and the cultural fashions of the time. As for national and international conflicts, and underlying social unrest, these were largely downplayed, as with the Paris demonstrations of June 1848.

However, *L’Illustration* differed from the broadsheets affiliated to political parties by its declared apoliticism, while maintaining a focus on the various types of current events. The weekly was tailored to the bourgeoisie who relied on political calm for their prosperity. An annual subscription in Paris cost 30 francs, increased in 1848 to 36 francs; in the provinces it cost 32 francs, before also being increased to 36 francs. This was only slightly less than a daily appearing seven times more often (40 francs). A single issue cost 75 centimes, compared with 10 centimes for *Le Magasin Pittoresque*. A subscription was equivalent to 210 hours of a provincial laborer’s wage. Launching an illustrated news weekly in 1843 could only work if it was favorably received by a bourgeoisie with solid incomes. There are several indicators of bias towards its Paris readership in *L’Illustration*. The “Paris Page” addressed the capital’s inhabitants directly, the art sections concentrated on the Paris scene, and single issues only went on sale in Paris. The profile of the typical reader was therefore that of the Paris bourgeois and his family.

A rapidly introduced “Readers’ Letters” section kept the publishers’ fingers on the readers’ pulse. Many readers offered ideas for cover stories or help in covering local events, although most offers reached the editors’ office after their newsworthiness had expired. Readers were plainly attracted by the images that were published. Their letters spoke of sending drawings, and donating collections of images to the weekly; they discussed the authenticity of prints, the choice of paintings, and the kind of images they would like to see in the paper. Such feedback only confirmed Charton, Paulin, and Dubochet in the foresightedness of their image-based enterprise.

Images: mixing enlightenment with pleasure

In 1843, the preface to the first volume of *L’Illustration*, entitled “Our purpose,” described images as a knowledge tool: “How pale, lifeless, persistently incomplete, and difficult to understand even the best of written descriptions can be, compared with showing things as they really are! It has long been recognized that ‘what reaches the mind via the ear is less easily retained than what reaches it via the eye’.”

Irrespective of a reader’s educational level, images facilitated access to knowledge by using what the weekly described as “this other language: [...] the pencil and the engraver’s chisel.” The lines of a drawing were considered as more accessible to human vision than the letters of a text, which require prior knowledge to be read. “*L’Illustration* will, from the outset, be truly what we intended it to be, a vast repository
A TOUCH OF FRANCE

L’Illustration and the birth of the French illustrated press – Gervais

The “engraving room” of *L’Illustration* (March 2, 1844, No. 53 issue). Teams of engravers worked 24 hours a day to produce the wood blocks for the generously illustrated journal. © *L’Illustration*/Keystone.

describing and depicting all the facts that contemporary history records in its annals, as they occur. [...] *L’Illustration* will, in a word, be a mirror faithfully reflecting [...] life in 19th-century society.”

The weekly justified the use of wood engraving as a way of so shortening the intellectual distance between spectator and subject that it came to reflect the news itself. Over and above the educational aspect, this use of images expressed a form of journalistic modernity that was also apparent in the editors’ textual policy. Although they did sometimes use news items from the Havas agency, they tended to avoid official sources, placing minimal reliance on intermediaries, and turning in preference to their network of regular correspondents—readers for the most part—and special correspondents, dispatched into the field. Reports and images had to demonstrate proximity to the event and mirror-like objectivity, enabling the paper to distance itself from the propagandist techniques of the partisan broadsheets. However, before the task of enlightenment could begin, the illustrations first had to attract readers and get them to buy. Images may have had a didactic function, but they also expressed the idea that there could be pleasure in acquiring knowledge. Far more than the other techniques that were mobilized to boost the circulation—social diary, serials, famous writers—images equated newspaper reading with pleasure.

Images in text

The increase in illustrated publications, whether periodicals or books, had prompted many French engravers to learn relief wood engraving. Imported by the English engraver Charles Thomson in 1816, this technique came into widespread use in the 1830s. The

Boxwood block with engraving of a “cockfight in Flanders.” After a painting by Rémi Cogghe (oil on canvas, 1889) now at the Musée d’Art et d’Industrie de Roubaix. For extra speed, several engravers would work on a single engraving, each on one of the smaller blocks that made up the final image. The smaller blocks were then assembled (notice the horizontal lines and the conspicuous vertical line). The engraving is so fine one hardly feels it when running a finger along the surface. After printing, blocks were scraped and reused many times. About 80 blocks are still preserved at the offices of *L’Illustration*. On the right: the printed outcome. Photos by Frédéric Joly. © *L’Illustration*/Keystone.
demand drove a tenfold increase in the number of engraving workshops; there were over 200 wood engravers by 1857. In the early 1840s the second generation of wood engravers became sufficiently well-organized and numerous to meet the demand without calling in English specialists. At its inception, \textit{L'Illustration} worked with just one studio: Andrew-Best-Leloir.

Unlike conventional woodcuts made in the sense of the grain, relief engraving against the grain used blocks sawn transversally to the trunk. Another difference was that the wood was not worked with the graver used for conventional woodcuts, but with a chisel of the kind used on metal. This technique remained just as fast, but was more akin to metalwork, and could produce many deft shades of gray. This was a definite advantage in artistic engraving, but also in reproducing paintings or photographs with many subtle shades. It made it possible to copy daguerreotypes. Also, in relief engraving the wood blocks were cut at the same height as print blocks, meaning that they did not have to be printed separately, but could be composed in a page for printing amidst typographic characters. In expert hands, images printed perfectly with text, thus “captivating at first glance,” according to a modern commentator, “and forcing the attention of the least attentive.” The result was an acceptable quality/cost/time-to-completion ratio, encouraging publishers to think up new objects to construct around the image and typesetters to develop a range of critical new skills.

\textbf{Text as a graphic component}

\textit{L'Illustration} was a 16-page broadsheet. Each page comprised three equal-width columns, separated by two vertical white-space gutters. A thicker horizontal white space separated each article from the next. Together with the title block, these white spaces organized the divisions between type. The text was in size 8 Garamond-like font, which was easy to read. Only on the advertisement page—the inside back page—were fonts, emboldenings, and type sizes varied to enliven the page presentation and attract the reader’s eye. Images greatly lightened the mass of text and were the main method of optimizing the transition between pages.

The flag, or paper title, was always accompanied by a full-width engraving and masthead showing the issue and volume numbers, date of publication, subscription charges, and publisher’s address, all of which occupied a third of the cover page. The following texts, list of contents and usually the “Story of the week” section were always squeezed by the accompanying image. Initially, engravings could vary in width, but always in line with the column margins. But as the years passed, they became freer, resulting in a less disciplined presentation. Although this made the text harder to read, it added to the overall graphic impact. Sometimes the text...
would be reduced to just a few lines, occupying a third of a column, becoming a graphic feature in its own right, setting off the engravings on the page. Text and images were combined to maximum effect on the illustrated page to astonish and captivate the reader-spectator.

To optimize their print quality, all images were set on the same surface, so that once the paper was folded they would be found on pages 1, 4, 5, 8, 9, 12, 13, and 16. Articles were in an order—or, as the paper once acknowledged, “disorder”—closely determined by the images. Layout was subject to printing constraints and dictated by the engravings. Text had to follow suit. Once set, image formats could not be changed; wood engravings could not be enlarged or reduced to comply with spatial constraints. Text, on the other hand, was malleable, and could be shortened or expanded. Articles could thus be divided into parts and published according to need in several issues. Every day, the editorial offices received “detailed reports and original drawings of all the important events that had happened during the week on the planet.” To feed their need for news, they transformed these facts into consumable events and elevated banal situations into picturesque engravings, practicing a version of journalism that they termed “news-ism.” Images and text were selection criteria of equal weight in informing editorial choice. If a drawing arrived too late to be engraved, the event was not mentioned. The same applied if the quality of a sketch failed to come up to editorial expectation. Images were a structural component that defined the illustrated newspaper.

Introduction of photography

From 1848 onwards, the words “From a photograph” began to appear beside the legends to certain engravings, becoming more frequent during the 1850s and weekly from 1858 onwards. Before half-tone engraving made it possible to mix text and image directly in the page layout, photographs had to transit through the engravers’ workshop before they could be published.

Of the images published in *L’Illustration* under the editorship of Paulin (1844-1859), 214 were engraved from a silver-plate image. In eight of these cases, the legend stated that they had been engraved from a daguerreotype. In the remainder, the wording is imprecise and the photographic technique difficult to identify. We know which proofs were supplied by Louis Désiré Blanquart-Évrard (1802-1872, who introduced the albumen paper print process) and the botanist Louis-Alphonse de Brébisson (1798-1872); these were paper prints. Most of the other original images were probably negatives on glass sensitized with collodion (nitrocellulose dissolved in ether). That *L’Illustration* used photographs at all is clearly of interest, but 214 is a paltry tally compared with the total engravings published from 1843 and 1859, estimated at between 19 800 and 26 400. The period between 1840 and 1870 was one of feverish experiment in photomechanical reproduction, involving some key figures in the early history of photography: the physicist Armand Fizeau (1819-1896), Abel Niépce de Saint-Victor (1805-1870), the nephew of Nicéphore Niépce...
and perhaps most celebrated of all, Nadar (1820-1910) in the rue Saint-Lazare. It is thus unrealistic at this stage to talk of a business partnership between the press and portrait photography. The relationship was not financial. *L’Illustration* received a batch of images every day from its correspondents for nominal amounts: the major investment was downstream, in the chain of draftsmen, engravers, and printers who processed the image for publication. A wood engraving, once completed, was a tradable asset in that it bypassed this chain. The engraving of Jenny Lind, published in Germany and France in 1850, was undoubtedly bought (or traded) by the *L’Illustration* from the *Illustrierte Zeitung*, which had published it a few days earlier.
Apart from such examples of trade in “image objects” in the early years of the illustrated press, the image as the subject of an illustration reached the paper for no fee. Whether amateurs or professionals, all photographers were credited. This detail was important for the paper, since some legends did not credit the author. Of all the images from this period, of whatever kind, 23 carry the byline “from a photograph.” Where the author was known, the name was given, not to add to reputation, but to authenticate the provenance of the image-based information involved. Whether textual or visual, news was more reliable if it came from the site of an event rather than from official sources. Naming an image’s author, even if obscure, together if possible with the location, offered guarantees in this regard. In some cases, only the location was given: “from photographic proofs sent from Saint Petersburg.” If neither name nor location could be given, it could still be published, provided it was used with the accompanying article. On the other hand, an image with clear subject and authenticated provenance could be published on its own, without an accompanying article.

Photographing events
Orchestrated festivities accounted for many of the images. Over one third of the engravings “from photographs” depicted “launches,” “arrivals” and “landings,” “openings” and “celebrations,” “maneuvers” and “parades,” and “banquets” and “receptions.” For photographers, the advantage in all these events was the absence of surprise: they were planned well in advance. Working with wetplate collodion or even a dry method required prior organization. Forewarned photographers had the time they needed to transport their equipment, prepare their chemistry, and select their viewpoint. The seconds required for exposure meant choosing an angle that would minimize the impact of movement. A photographer needing to avoid a blurred image could never approach his subject as closely as could a draftsman. Draftsmen could adopt photographers’ solutions to the technical constraints of their medium, but a photograph could not produce as many effects as a drawing.
The 1843 preface, “Our purpose,” proclaimed the editors’ interest in “news items whose disaster proportions demand a pencil to reproduce them exactly for the mind.” Fifteen engravings “from a photograph” depicted catastrophes affecting buildings and landscapes. From Florence, the Alinari brothers, founders of the world’s oldest extant photography laboratory, sent a view of the town of San Stefano under water; Alphonse Bernoud (1820-1875) provided nine photographs of an earthquake in Naples, while a “Mr Martin” in the Balearic Islands sent in a picture of the ruins “of Palma theater after a fire,” (see page 103). Photographers were at their greatest disadvantage under these conditions. Such events were sudden in onset and full of movement, thus doubly unsuited for recording on silver plate. They could be depicted only in terms of their aftermaths—ruined buildings and desolate landscapes—leaving the reader’s imagination to reconstruct the instants of unrecordable climactic tragedy—rumbling earthquake or searing flames—which had brought them about. The engravings of catastrophes from photographs were thus pictures of non-events.

Drawing or photography?
It was, and remains, difficult to identify the technique at the origin of an uncredited illustration. Some of the subtle features of engravings “from photographs” are caused by problems that photographers managed to circumvent. But in addition to the technical constraints of photography, there was also the input from draftsman and engraver that tended to make all illustrations look the same, irrespective of their origin. These artisans reshaped the silver image, touching up adjustments and additions in pencil and crayon, and chiseling the wealth of photographic half-tones into close-knit hatchings. The wetplate collodion method was more sensitive than the daguerreotype, but still did not allow photographers to take pictures involving movement. Unless several extreme conditions could be met simultaneously, “live” photography was unusual in this period. Conventional engravings, on the other hand, had typically been “live” since the beginning of the 19th century. When draftsmen trained in this tradition touched up photographers’ images, they only added to the confusion over the technical origin of uncredited engravings published in L’Illustration. The only sure way of telling a photograph from a drawing was to refer to the legend. Initially, legends gave only the subject of the image. Subsequently they added information on provenance. Just as the author’s name and location offered credibility, so the legend certified the technical origin of the engraving—all the more usefully in the case of photographs, since the difference was otherwise invisible.

This being the case, why did illustrated papers use photographs as an image source at all? Visually, engravings “from photographs” differed little, if at all, from those inspired by a drawing or painting. Legends stating the technical origin were not specific to photographs. They provided the same information about author, location, and technique in the case of drawings and paintings too. To think that considerations of photographic authenticity governed image selection by the editors is a modern take, with no relevance to the thinking of the time. Engravings “from photographs” may well have represented the entry of the new medium into the illustrated press, but their informational value did not exceed that of a drawing. In addition, we now tend to underestimate the entertainment function of the image that underpinned the entire illustrated newspaper enterprise.

According to statistics from the 1860s, the number of engravings from photographs used in L’Illustration increased to 1865, then fell to 1870, during which period wood engraving remained unchallenged in periodical illustration. Could it be that the press had already ceased to believe that photography offered added informational value?

The editors did not choose photographs at the expense of drawings, but simply accepted them from their image providers. Paintings, drawings, and photographs were so many variants of a single Image species, whose function was to charm the readership. Photographs offered a manageable compromise: wood engraving took rather longer, but at no substantial additional cost. The legends too fitted in with the paper’s general dynamic.
From its first issue onwards, *L'Illustration* was intent on developing a new form of journalism based on a network of regular and special correspondents. This illustrated “news-ism” set itself apart from the conventional press by spurning official news sources. Crediting author, location and technique in their legends was one way for the editors to proclaim the independence of their sources, enhance their credibility, and mask the underlying entertainment function of their images.

**News or information?**
The author of the 1843 preface preferred the term “news” to that of “information,” and its corollary “news-ism” to that of journalism. Although news and information were alike in that both were an assemblage of facts about someone or something, news had no sense of research or enquiry, unlike information, which presupposed some notion of both. *L'Illustration* offered its images as an alternative path to knowledge. Easier than conventional written communication, this path was based on the premise that illustrations were instantly intelligible. The power accorded to images created a belief in their impartiality, based on the relationship of trust established between them and the reader. In its desire to be independent of the official sources of information, *L'Illustration* constructed the idea of credible “news-ism.” There was nothing inevitable about its encounter with photography. It was the product of market conditions that forced papers to expand their readership by offering something new: the illustrated weekly. To what extent images helped to transform the press of opinion into the press of information remains to be defined.


**FURTHER READING**

And then there was color. *L’Illustration* was soon to treat its readers with a lavish use of color, first for engravings and lithographs, and ultimately by introducing color photography. Shown here is the cover of the Christmas 1896 issue of *L’Illustration* with a color lithograph by Mucha. Photo by Frédéric Joly. © *L’Illustration*/Keystone.

*L’Illustration* and the birth of the French illustrated press – Gervais
Avec l’avènement quasi simultané en Europe de la presse illustrée d’actualité, la seconde moitié du XIXᵉ siècle fut le théâtre d’une véritable révolution dans le domaine de la presse écrite. Si la fonction satirique de la gravure connaissait depuis longtemps un succès dans la presse, ainsi Charivari, à partir des années 1840, des journaux proposent un usage séduisant et didactique de l’image d’actualité. Le coup d’envoi de ce nouveau processus d’illustration dans la presse hebdomadaire fut donné par l’Illustrated London News (Angleterre, 1842 et encore publié de nos jours), suivi l’année d’après par L’Illustration (France, 1843 jusqu’en 1944) et l’Illustrierte Zeitung (Leipzig, Allemagne, 1843 à 1940), puis par de nombreux autres journaux illustrés de par le monde dans les années 1860. Cet essor de la presse obligea les rédactions de l’époque à employer jour et nuit de véritables équipes de dessinateurs et de graveurs et bientôt de photographes. L’Illustration, fondée par Édouard Charton, Jean-Baptiste Paulin et Alexandre Dubochet, connut un succès immédiat et s’attacha des dizaines de milliers de lecteurs grâce à la qualité d’impression de ses gravures, à la richesse de ses informations, à la collaboration d’un réseau de correspondants et à la place toujours plus grande donnée à l’image. Pour l’essentiel les gravures sont majoritairement réalisées à partir de dessins, mais L’Illustration utilise rapidement des photographies (dès 1848), bien que celles-ci doivent passer, dans un premier temps, par les mains d’un graveur pour être reproduites dans les pages du journal (il faudra attendre les années 1890 pour que les procédés tramés permettent de reproduire mécaniquement la photographie). La collection de L’Illustration offre un panorama complet de la vie sociale, politique, scientifique et culturelle du XIXᵉ siècle. Chaque numéro était lu avec passion par les lecteurs d’alors et L’Illustration est désormais recherchée avec ardeur par les collectionneurs dans les foires aux livres et les brocantes. L’Illustration joue un rôle essentiel dans l’histoire de la presse française et doit être envisagée comme un élément fondateur de l’ère médiatique qui caractérise notre société contemporaine.
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