“Chance favors only the prepared mind”
Pasteur

New insights into \( I_f \) inhibition: from ischemia prevention to improvement in coronary outcomes
New insights into $I_f$ inhibition: from ischemia prevention to improvement in coronary outcomes

**EDITORIAL**

337  $I_f$ inhibition: breaking new ground in the treatment of stable coronary artery disease. *Inhibition du courant $I_f$: une innovation dans le traitement de la maladie coronaire stable*

R. Ferrari and K. Fox, Italy and United Kingdom

**THEMED ARTICLES**

343  The global burden of coronary heart disease

G. G. De Backer, Belgium

349  Heart rate: from risk marker to risk factor in coronary artery disease

J. S. Borer, USA

356  Elevated heart rate and atherosclerosis: pathophysiology and clinical outcomes

M. Böhm, J.-C. Reil, and F. Custodis, Germany

364  Is heart rate optimally controlled in patients with coronary artery disease in clinical practice?

C. Daly, Ireland

371  The place of ivabradine in the management of patients with CAD: new insights

P. G. Steg and G. Ducrocq, France

377  Lessons from BEAUTIFUL: new frontiers in heart rate control

Å. Hjalmarson, Sweden

384  Optimizing secondary prevention treatment in stable coronary artery disease

L. R. Padial, Spain
CONTROVERSIAL QUESTION
393 To what extent has monitoring of heart rate reduction in your coronary patients become part of your daily practice?

PROCORALAN
403 Clinical benefits of pure heart rate reduction with Procoralan: evidence and perspectives
I. Elyubaeva, France

INTERVIEW
410 The clinical implication of pure heart rate reduction in CAD management: future directions
K. Fox, United Kingdom

FOCUS
414 Recommendations on how to measure resting heart rate
P. Palatini, Italy

UPDATE
420 Prevention of endothelial dysfunction with pure heart rate reduction
J. Yang and J. -C. Tardif, Canada

A TOUCH OF FRANCE
430 The heart of the kings of France: “cordial immortality”
C. Régnier, France

440 The Cathedral Basilica of Saint-Denis
I. Spaak, France
Coronary artery disease (CAD) is today the leading cause of mortality worldwide, and it continues to be a major burden upon public health. Despite falling CAD mortality rates in Western European countries, the number of CAD patients may actually be increasing as a result of aging populations and the improving prognosis for coronary patients, the latter due to more effective treatments for acute coronary syndrome and revascularization, and improved prevention. CAD is expected to remain the world’s leading cause of disease burden (which represents aggregate mortality and morbidity) in 2020, despite considerable progress in prevention and treatment over the past 20 years.

Despite marked advances in primary and secondary prevention, several unmet needs remain in CAD management. Current guidelines recommend a two-pronged management strategy for patients with stable CAD, who require one treatment to relieve symptoms alongside another to reduce long-term morbidity and mortality. Despite the progress in the field, for various reasons that include inappropriate drug dosage and patient nonadherence to treatment schedules, many patients in clinical practice do not reach therapeutic goals. In addition, the optimization of treatment can be hindered by insufficient efficacy in patients with refractory angina and by a long list of medication contraindications. Another factor is poor tolerability, which may lead to treatment discontinuation and a reduction in the efficacy of even the most rigorous management strategy.

The results of the Clinical Outcomes Utilizing Revascularization and Aggressive drug Evaluation (COURAGE) trial show no extra benefit in terms of all-cause mortality, myocardial infarction, or other major cardiovascular events, with addition of percutaneous coronary intervention (PCI) in stable CAD patients receiving optimized medical therapy. Furthermore, interventions are not always possible, and most revascularized patients still require anti-ischemic/antianginal treatment after the procedure.

Clearly, these factors indicate the importance of developing novel therapeutic approaches that can improve CAD management. Heart rate is one of the clinical parameters that is most frequently assessed in daily practice. As it is the main determinant of ischemia, heart rate reduction is an established important therapeutic strategy in the prevention of ischemia. A strong association between elevated heart rate and increased risk of total and cardiovascular mortality has been shown in the general population, as well as in patients with hypertension, diabetes, and CAD. Experimental data have demonstrated the involvement of heart rate in the devel-
Ivabradine: benefits of heart rate reduction via selective If inhibition

An agent acting through heart rate reduction per se is an attractive solution; however, until recently, selective heart rate reduction was not possible, and exploratory and clinical work in this respect was challenging. Research during the past two decades with drugs that solely target heart rate control mechanisms has led to the development of several agents that interact with ion channels associated only with sinoatrial diastolic depolarization. The pharmacology of such selective heart rate–lowering agents is based on the finding more than 25 years ago that the If pacemaker current has a central role in modulating the rate of spontaneous diastolic depolarization in the sinoatrial node.8 The first agent approved in this class, ivabradine, has successfully entered the therapeutic armamentarium.

Ivabradine provides selective heart rate reduction without other hemodynamic effects. Firstly, it acts specifically on the sinus node cells on which f-channels are located, which are responsible for the diastolic depolarization in the sinus node action potential.9 Ivabradine selectively and concentration-dependently inhibits the If current. As a result of its selective heart rate reduction, ivabradine preserves contractility and maintains left ventricular relaxation during exercise.9 Importantly, the heart rate reduction produced by ivabradine is not associated with negative isotropic activity. Finally, contrary to β-blockade, it allows dilation of the coronary artery during exercise, thus preventing further ischemia.10 With ivabradine, the full benefit of prolonged diastole also results in enhanced coronary blood flow, with maximum oxygen supply to the subendocardial layers of the myocardium that suffer most from ischemia.

Clearly, for patients with stable CAD, these advantages of the mechanism of action of ivabradine provide the opportunity to attain the full clinical benefits of heart rate reduction without the counterproductive or deleterious cardiovascular actions that may accompany other heart rate–lowering agents. The antianginal and anti-ischemic efficacy of ivabradine has been demonstrated in clinical programs involving more than 5000 patients, focused around several international, multicenter, randomized, double-blind trials. In these trials, the antianginal and anti-ischemic efficacy of ivabradine was demonstrated compared with placebo11 and with active treatments such as β-blockers and calcium channel blockers.12,13 Furthermore, the long-term safety and efficacy of ivabradine was confirmed in a 1-year trial.14 Recently, in the trial ASSOCIATE (evaluation of the Antianginal efficacy and Safety of the aS-sociation Of the If Current Inhibitor ivAbradine with a beTa-blockEr), it was clearly demonstrated that in patients with stable angina receiving the β-blocker atenolol, ivabradine provides a significant improvement in total exercise duration.15 Whether the clinical benefits of ivabradine extend to beyond the prevention of angina was investigated in BEAUTIFUL (morBidity-mortality EvAlUaTion of the If inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction).

BEAUTIFUL: a new frontier in the treatment of stable CAD

The results of BEAUTIFUL open up promising opportunities in the management of CAD. BEAUTIFUL was a randomized, double-blind, placebo-controlled outcome trial conducted in 781 centers worldwide, which enrolled 10,917 eligible patients with documented CAD and left ventricular dysfunction.16 The mean baseline heart rate was 71.6 beats per minute (bpm). Use of cardiovascular medications recommended in current guidelines was high: 94% of patients were receiving aspirin or an anticoagulant, 74% were receiving statins, and 90% an angiotensin-converting enzyme inhibitor or an angiotensin II receptor blocker. A total of 87% of patients were receiving β-blockers.

BEAUTIFUL has provided answers to some important questions relating to the prognostic importance of heart rate, and to the importance of heart rate reduction with ivabradine for reduction of cardiovascular events in CAD patients with left ventricular dysfunction. The rationale behind BEAUTIFUL is that raised resting heart rate is a risk factor for cardiovascular and total mortality. Indeed, resting heart rate is receiving increasing recognition as a risk factor for cardiovascular outcomes and mortality.17 Most of the evidence for this, however, has come from epidemiological studies. The BEAUTIFUL investigators have added substantially to current knowledge concerning the prognostic value of elevated heart rate. The placebo arm of BEAUTIFUL provided a large coronary population who were well treated in terms of cardiovascular prevention. This provided an exceptional opportunity to prospectively test the predictive value of resting heart rate by analyzing the effect of elevated values at baseline on outcomes in the placebo group (n=5438).18 The results showed that elevated resting heart rate (≥70 bpm) is a strong predictor of outcome in patients with stable CAD and left ventricular dysfunction. This was the case for all of the outcomes assessed in the study. Patients in the subgroup with resting heart rate ≥70 bpm were 34% more likely to die from cardiovascular causes (hazard ratio [HR], 1.34; 95% confidence interval [CI], 1.10–1.56; P=0.0041) and 53% more likely to be hospitalized for new or worsening heart failure (HR, 1.53; 95% CI, 1.25–1.88; P<0.0001) than those with values <70 bpm. Similarly, elevated heart rate was associated with a 46% increased risk of fatal and nonfatal myocardial infarction (HR, 1.46; 95% CI, 1.11–1.91; P=0.0066).
and a 38% increase in the need for coronary revascularization (HR, 1.38; 95% CI, 1.02-1.86; P=0.037). These data were adjusted for all the variables that differed between the two groups at baseline, including β-blocker intake and other background therapy.

The BEAUTIFUL results confirm the retrospectively-produced results of previous studies in the general population and in normotensive and hypertensive CAD patients. They also constitute the first clear demonstration that an elevated resting heart rate (≥70 bpm) places patients at risk for cardiovascular events, even if they are indeed well treated according to current guidelines, including treatment with β-blockers. Thus, the important implication from BEAUTIFUL is that an elevated heart rate just above 70 bpm is deleterious in patients with stable CAD and needs to be corrected.

BEAUTIFUL investigated the effect of ivabradine on outcomes in stable CAD patients.16 Ivabradine reduced mean resting heart rate to 61 bpm after 30 days; mean resting heart rate remained low thereafter, and was 64 bpm at the end of the study. There was a 6.4-bpm difference between the ivabradine and placebo groups at 6 months, and a 5.6-bpm difference at 2 years. Ivabradine did not affect the primary composite end point. However, in patients with a heart rate of 70 bpm or greater, ivabradine had a significant impact on all end points linked to coronary events. There was a 36% reduc-

tion in the relative risk of hospitalization for fatal and nonfatal myocardial infarction in the patients treated with ivabradine (HR, 0.64; 95% CI, 0.49-0.84; P=0.001) and a 30% relative risk reduction for coronary revascularization (HR, 0.70; 95% CI, 0.52-0.93; P=0.016). The reduction in the relative risk of coronary revascularization applied to both PCI and coronary artery bypass graft (CABG); patients treated with ivabradine had a lower annual incidence of PCI (1.29 versus 1.61 per 100 patient-years) and CABG (0.47 versus 0.55 per 100 patient-years) than patients in the placebo arm. Treatment with ivabradine was also associated with a 22% reduction in the relative risk of a composite end point of hospitalization for fatal and nonfatal myocardial infarction and unstable angina pectoris (HR, 0.78; 95% CI, 0.52-0.93; P=0.023). These benefits on coronary outcomes were observed in patients receiving optimal background treatment, including β-blockers (84% of patients). The results also demonstrate that ivabradine can be safely prescribed to patients with stable CAD and left ventricular dysfunction, including those receiving a β-blocker.

The results of BEAUTIFUL extend the efficacy of ivabradine in improving the symptoms of angina to efficacy in reducing the risk of coronary events in a broader stable CAD population with increased resting heart rate. This new evidence opens up promising opportunities in the management of stable CAD.

References
14. López-Bescós L, Filippova S, Martos R. Long-term safety and efficacy of ivabra-
16. Fox K, Ferrari R, Tendera M, et al. BEAUTIFUL Steering Committee. Rationale and design of a randomized, double-blind, placebo-controlled trial of ivabradine in patients with stable coronary artery disease and left ventricular systolic dys-
function: the morbidity mortality Eula1a1on of the I inhibitor ivabradine in pa-
17. Fox K, Ford I, Steg PG, Tendera M, Robertson M, Ferrari R. Heart rate as a prognostic risk factor in patients with coronary artery disease and left-ventricu-

Keywords: coronary artery disease; left ventricular dysfunction; resting heart rate; risk factor; coronary event reduction; ivabradine.

I inhibition: breaking new ground in the treatment of stable CAD – Ferrari and Fox
La maladie coronaire (MC) constitue aujourd'hui la principale cause de mortalité à travers le monde, et représente toujours une charge importante pour la santé publique. Malgré une diminution des taux de mortalité par MC dans les pays d'Europe occidentale, le nombre de patients coronariens serait en fait en augmentation à la suite du vieillissement de la population et de l'amélioration du pronostic des patients coronariens due à des traitements plus efficaces du syndrome coronaire aigu et de la revascularisation, et à une amélioration de la prévention. Malgré des progrès considérables obtenus dans le domaine de la prévention et du traitement de la MC au cours des 20 dernières années, il est vraisemblable qu'elle constitue encore en 2020 la cause majeure de mortalité et de morbidité dans le monde.

Malgré d'importantes avancées en prévention primaire et secondaire le traitement de la MC reste encore incomplet. Les directives actuelles recommandent une stratégie thérapeutique double pour les patients atteints de MC stable, composée d'un traitement destiné à soulager les symptômes parallèlement à un autre visant à réduire la morbidité et la mortalité à long terme. Malgré les progrès accomplis dans ce domaine, de nombreux patients n'atteignent pas en pratique clinique les objectifs thérapeutiques pour différentes raisons, comme une posologie inappropriée des médicaments et la nonobservance des protocoles thérapeutiques par les patients. En outre, l'optimisation du traitement peut être entravée par une efficacité insuffisante chez les patients atteints d'angor réfractaire, et par une longue liste de contre-indications médicamenteuses, ou encore par une mauvaise tolérance, qui peut entraîner une interruption du traitement et une réduction de l'efficacité même pour une stratégie thérapeutique des plus rigoureuses. Les résultats de l'étude COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive druG Evaluation) montrent qu'aucun bénéfice supplémentaire sur la mortalité de toutes causes, l'infarctus du myocarde et les autres événements cardio-vasculaires majeurs n'est apporté par la réalisation d'une intervention coronaire percutanée chez des patients atteints de MC stable recevant un traitement médicamenteux optimisé. En outre, les interventions ne sont pas toujours possibles, et la plupart des patients ayant subi une revascularisation nécessitent toujours un traitement anti-ischémie/antiangineux après la procédure.

Ces facteurs indiquent clairement l'importance de développer de nouvelles approches thérapeutiques susceptibles d'améliorer la prise en charge de la MC. La fréquence cardiaque est l'un des paramètres cliniques les plus fréquemment évalués en pratique quotidienne. Étant le principal déterminant de l'ischémie, une ré-

Inhibition du courant If : une innovation dans le traitement de la maladie coronaire stable
par R. Ferrari et K. Fox, Italie et Royaume-Uni
Il apparaît clairement que les avantages apportés par le mécanisme d’action de l’ivabradine permettent aux patients atteints de MC stable de recueillir tous les bénéfices cliniques d’une réduction de la fréquence cardiaque, sans avoir à subir les actions cardio-vasculaires contre-productives ou nocives qui peuvent caractériser d’autres produits abaissant la fréquence cardiaque. L’efficacité antianginuse et anti-ischémique de l’ivabradine a été démontrée dans des programmes cliniques portant sur plus de 5 000 patients, centrés sur plusieurs études internationales randomisées, multicentriques et en double aveugle. Dans ces études, l’efficacité antianginuse et anti-ischémique de l’ivabradine a été démontrée par rapport à un placebo, et à des traitements actifs, notamment des bétabloquants et des inhibiteurs calciques. En outre, la sécurité d’emploi et l’efficacité à long terme de l’ivabradine ont été confirmées au cours d’une étude de 1 an. Récemment, il a été démontré dans l’étude ASSOCIATE (evaluation of the Antianginal efficacy and Safety of the aSSociation Of the I, Current Inhibitor ivAbradine with a beta-blockEt) que, chez les patients atteints d’angor stable recevant un traitement par l’atenolol, un bétabloquant, l’ivabradine améliorait significativement la durée totale de l’effort. L’étude BEAUTIFUL (morBidity-mortality EvAlUaTion of the aSSociation Of the I with a Beta-Inhibitor ivAbradine in patients with coronary disease and left ventricular dysfunction) a exploré si les bénéfices cliniques de l’ivabradine dépassaient la simple prévention de l’angor.

Étude BEAUTIFUL : un nouvel horizon dans le traitement de la maladie coronaire stable

Les résultats de l’étude BEAUTIFUL sont prometteurs pour la prise en charge de la MC stable. L’étude BEAUTIFUL, randomisée, en double aveugle, contrôlée contre placebo, a été menée dans 781 centres à travers le monde, et a inclus 10 917 patients admissibles présentant une MC stable et un trouble ventriculaire gauche documentés. La fréquence cardiaque initiale moyenne était de 71,6 battements par minute. Les traitements cardio-vasculaires recommandés par les directives actuelles ont été très suivis : 94 % des patients recevaient de l’aspirine ou un anticoagulant, 74 % recevaient des statines, 90 % un inhibiteur de l’enzyme de conversion de l’angiotensine ou un antagoniste des récepteurs de l’angiotensine II. Au total, 87 % des patients étaient traités par des bétabloquants.

L’étude BEAUTIFUL a répondu aux questions essentielles concernant l’importance pronostique de la fréquence cardiaque, et le rôle d’une diminution de la fréquence cardiaque par l’ivabradine dans la réduction des événements cardio-vasculaires des patients atteints de MC et de trouble ventriculaire gauche. La justification de l’étude BEAUTIFUL résidait dans le fait qu’une fréquence cardiaque élevée au repos est un facteur de risque de mortalité cardio-vasculaire et totale. En effet, une fréquence cardiaque au repos élevée est considérée de plus en plus souvent comme un facteur de risque d’événements cardio-vasculaires et de mortalité car-
dio-vasculaire\textsuperscript{6}, ce qui est toutefois prouvé par des études épidermologiques. Les investigateurs de l'étude BEAUTIFUL ont considérablement amélioré les connaissances actuelles sur la valeur pronostique d’une fréquence cardiaque élevée. Une importante population de patients coronariens bien traités en termes de prévention cardio-vasculaire faisait partie du bras placebo de l'étude BEAUTIFUL, ce qui a permis d’évaluer de façon prospective la valeur prédictive de la fréquence cardiaque au repos, en analysant les effets sur les résultats du groupe placebo (n = 5 438) d’une valeur élevée à l’inclusion\textsuperscript{17}. Les résultats ont montré qu’une augmentation de la fréquence cardiaque au repos (\(\geq 70\) bpm) constituait un facteur prédictif fiable de l’évolution des patients atteints de MC stable et de trouble ventriculaire gauche, ce qui a été vérifié pour toutes les données de l’étude. Les patients du sous-groupe dont la fréquence cardiaque au repos était \(\geq 70\) bpm présentaient une augmentation de 34 % du risque de mortalité cardio-vasculaire (risque relatif [RR] : 1,34 ; intervalle de confiance [IC] à 95 % : 1,10 - 1,66 ; p = 0,0041) et une augmentation de 53 % de la probabilité d’être hospitalisé pour l’apparition ou l’aggravation d’une insuffisance cardiaque (RR : 1,53 ; IC à 95 % : 1,25 - 1,88 ; p < 0,001) par rapport à ceux dont les valeurs étaient < 70 bpm. De même, une augmentation de la fréquence cardiaque a été associée à une aggravation de 46 % des risques d’infarctus du myocarde fatal et non fatal (RR : 1,48 ; IC à 95 % : 1,11 - 1,91 ; p = 0,0066) et une augmentation de 36 % du besoin d’une revascularisation coronaire (RR : 1,38 ; IC à 95 % : 1,02 - 1,86 ; p = 0,037). Ces données ont été ajustées pour toutes les variables qui différaient à l’inclusion entre les deux groupes, notamment la prise de bêtabloquants ou d’un autre traitement de fond.

Les données de l’étude BEAUTIFUL confirment les résultats rétrospectifs de précédentes études sur la population générale et sur des patients coronariens normotendus et hyperlndus. Ils confirment aussi clairement qu’une augmentation de la fréquence cardiaque au repos (\(\geq 70\) bpm) expose les patients à un risque d’événements cardio-vasculaires, même s’ils sont convenablement traités conformément aux directives actuelles, et reçoivent notamment un traitement par les bêtabloquants. La conséquence importante de l’étude BEAUTIFUL est qu’une augmentation de la fréquence cardiaque au-dessus de 70 bpm est nocive pour les patients atteints de MC stable, et qu’elle doit être corrigée.

L’étude BEAUTIFUL a analysé les effets de l’ivabradine sur l’évolution des patients atteints de MC stable\textsuperscript{18}. L’ivabradine a réduit la fréquence cardiaque moyenne au repos à une valeur de 61 bpm après 30 jours, elle est restée faible par la suite, pour atteindre une valeur de 64 bpm à la fin de l’étude. Une différence de 6,4 bpm a été observée entre les groupes ivabradine et placebo à 6 mois, et une différence de 5,6 bpm après 2 ans. L’ivabradine n’a pas affecté le critère composite principal. Cependant, chez les patients présentant une fréquence cardiaque au moins égale à 70 bpm, l’ivabradine a exercé un impact significatif sur tous les paramètres liés aux événements coronaires. Une réduction de 36 % du risque relatif d’hospitalisation pour infarctus du myocarde fatal et non fatal a été observée chez les patients traités par l’ivabradine (RR : 0,64 ; IC à 95 % : 0,49 - 0,84 ; p = 0,001) et une réduction de 30 % du risque relatif de revascularisation coronaire (RR : 0,70 ; IC à 95 % : 0,52 - 0,93 ; p = 0,016). La réduction du risque relatif de revascularisation coronaire s’est appliquée à la fois aux interventions coronaires percutanées et aux pontages aortocoronaires : les patients traités par l’ivabradine ont présenté une incidence annuelle plus faible d’intervention coronaire percutanée (1,29 contre 1,61 pour 100 années-patient) et de pontage (0,47 contre 0,55 pour cent années-patient) que les patients du bras placebo. Le traitement par l’ivabradine a également été associé à une réduction de 22 % du risque relatif d’un paramètre composite associant l’hospitalisation pour infarctus du myocarde fatal et non fatal et l’angor instable (RR : 0,78 ; IC à 95 % : 0,52 - 0,93 ; p = 0,023). Ces bénéfices sur les résultats coronaires ont été observés chez des patients recevant un traitement de fond optimal, comprenant des bêtabloquants (84 % des patients). Les résultats ont également mis en évidence que l’ivabradine pouvait être prescrite sans risque chez des patients présentant une MC stable et un trouble ventriculaire gauche, notamment ceux traités par bêtabloquant.

The global burden of coronary heart disease

by G. G. De Backer, Belgium

The coronary heart disease (CHD) epidemic has been extremely dynamic over the last half century, with marked variation in its characteristics among different regions of the world—both between neighboring nations and even regions within a country. In the USA and most countries of the European Union, the age-standardized CHD mortality rates have decreased significantly; this may lead paradoxically to an increase in the prevalence of CHD in these countries—indeed, better survival of CHD patients and demographic changes have resulted in more elderly people suffering from CHD. In other parts of the world, the incidence of CHD is still on the increase, and it is estimated that in the coming years the number of CHD patients will increase substantially, especially in developing and transitional countries. Recent developments in the epidemic in the USA and Europe additionally suggest that the spectacular decline in CHD in the last half of the 20th century may have halted, especially in younger subjects. CHD is also an important source of disability, which can be translated into disability-adjusted life years (DALYs). The CHD burden in terms of DALYs is also projected to rise in the coming years, especially in countries in transition. There are also important regional differences in CHD burden within countries. If these differences are well understood, lessons can be learned and the knowledge applied in order to reduce the burden in less well-off communities.

Coronary heart disease (CHD) is now the leading cause of death worldwide; it is on the rise and has become a true pandemic that respects no borders.” This statement, made in 2009, can be found on the Web site of the World Health Organization, and is not that different from the warning issued in 1969 by the executive board of the World Health Organization: “Mankind’s greatest epidemic: coronary heart disease has reached enormous proportions striking more and more at younger subjects. It will result in coming years in the greatest epidemic mankind has faced unless we are able to reverse the trend by concentrat-ed research into its cause and prevention.”

This may give the wrong impression that nothing has changed over the last 40 years. On the contrary, the epidemic of CHD has been, and still is, extremely dynamic and influenced by environmental factors, resulting in rises and falls in morbidity and mortality over relatively short time periods. Furthermore, during the last 40 years, results from observational and intervention studies have clearly shown that CHD is partial-
ly preventable. Knowledge of this has been implemented in some populations more than in others, which may explain the heterogeneous changes that have taken place in CHD incidence and mortality among different places around the world.

The underlying pathology of most clinical manifestations of CHD is atherosclerosis; this is a slowly progressive process that starts in the young. Despite the progress that has been made toward prevention and cure of CHD, it appears that our actual abilities are limited to a retardation of atherosclerosis and a postponement of CHD to older age; given the demographic changes that are taking place in most communities, one has to expect a further increase in the absolute number of people with CHD.

The purpose of this article is to describe aspects of the CHD epidemic in relation to time, place, age, and gender. From this, one can learn lessons about how to prevent CHD, or at least how to reduce the number of premature deaths and improve quality of life, thus prolonging life expectancy in good health and reducing the number of disability-adjusted life years (DALYs).

The global burden of coronary heart disease – The burden of coronary heart disease at the global level

CHD has received great attention because its epidemic development after World War II initially struck the industrialized countries. Nowadays, however, the burden of CHD involves the whole world; the age-standardized death rates for CHD are declining in many developed countries but are increasing in developing and transitional countries — partly as a result of demographic changes, urbanization, and lifestyle changes. Today, approximately 3.8 million men and 3.4 million women worldwide die each year from CHD. According to the Global Burden of Disease Study, the developing countries contributed 3.5 million of the 6.2 million global deaths from CHD in 1990. The projections estimate that these countries will account for 7.8 million of the 11.1 million deaths due to CHD in 2020.

But there is more to these numbers when they are translated into health care and community costs. In 2003, the economic impact of cardiovascular disease (CVD) on health care costs in the enlarged European Union (EU) was estimated to be 169 billion euros, which is an average of 3724 euros per capita per year. A total of 62% of this sum was related to direct costs and 21% to productivity loss. The latter is particularly important in developing countries; indeed, given the demographic composition of the populations of developing countries and the changes that will take place in age distribution, not only is the increase in CVD alarming in itself, but also the fact that this increase in the coming decades will manifest itself mainly in the economically active part of societies.

In 1990, 47% of all CVD-related deaths in developing countries occurred before the age of 70 years, in contrast with only 23% in high-income industrialized countries. This has a consequence in that there is a difference in the number of DALYs resulting from CVD; the burden of CVD expressed in DALYs from 1990 to 2020 was estimated for different populations in the Global Burden of Disease Study. In India and China, a spectacular rise in the number of DALYs is expected in the coming years — from a figure of less than 25 million DALYs in each country in 1990, to 30 million and 35 million in India and China, respectively, in 2020. By contrast, a decline from around 20 million to 15 million DALYs is expected in established market economies. The gap between industrialized countries and developing countries will significantly increase, and the increasing burden of CVD in terms of DALYs will clearly mostly affect developing countries in the next two decades. In different parts of the world, the dynamics of the CHD epidemic are also very different in terms of pattern, magnitude, and timing.

The burden of coronary heart disease in the USA – The burden of coronary heart disease in the USA

CHD mortality in the USA began to decline in the mid 1960s. Age-adjusted CHD mortality rates continued to fall throughout the 1990s, although crude mortality rates changed more modestly, with CHD being postponed and manifesting itself at an older age. Because of this, CHD remains the largest single cause of death and disability in the USA. In 2005, CHD caused approximately 1 of every 5 deaths in the USA. It is the largest major killer of both American men and women. Approximately 37% of people who develop a coronary event in a given year will die from it.

Results from the Framingham study based on observations from 1950 until 1999 demonstrate that CHD death rates decreased by 59% during this time period. This favorable trend was seen in men and women. From 1990 to 2005, the death rate from CHD declined by 34.3%. In 2005, the overall CHD death rate was 144.4 per 100 000 population. For white males it was 187.7 and for black males it was 213.9 per 100 000, and for white females the rate was 110.0 and for black females 140.9 per 100 000.
According to data from the National Registry of Myocardial Infarction, the in-hospital mortality rate for an acute myocardial infarction declined from 11.2% in 1990 to 9.4% in 1999. Analysis of CHD mortality data among US adults aged 35 to 54 years showed that the annual percentage change in (age-adjusted) mortality rates slowed markedly from 1980 to 2002 in both men and women. Particularly noteworthy is that the mortality rate among women aged 34 to 44 years of age has been increasing on average by 1.3% per year since 1997.

With regard to incidence, data from the Atherosclerosis Risk in Communities (ARIC) and Cardiovascular Health Study indicate that annually, 785,000 Americans have a new coronary attack and 470,000 have a recurrent attack; in addition, approximately 195,000 silent myocardial infarctions occur each year. This assumes that 21% of the 935,000 first and recurrent myocardial infarctions are silent.

On the basis of results from the Framingham study, it is estimated that CHD accounts for more than half of all cardiovascular events in men and women under 75 years of age. The lifetime risk of developing CHD after the age of 40 years is 49% in men and 32% in women. The total incidence of coronary artery disease (CAD) morbidity data from the latest available year. CHD, coronary heart disease; CVD, cardiovascular disease. Based on data from reference 15.

The burden of coronary heart disease in Europe

Mortality burden
CHD by itself is the single most common cause of death in Europe and the EU. Between 1 in 5 and 1 in 7 women die from CHD in Europe and the EU, and in men, it accounts for between 1 in 4 and 1 in 6 of all deaths. One could argue that this is the fate of communities that are growing to very old ages. This may be part of the explanation. In 2005, the mean life expectancy at the age of 50 years for men and women in all 25 EU countries was 28.6 and 33.5 years, respectively. Therefore, dying before the age of 75 years in an EU country may be considered as premature. In Figure 1, EU deaths under the age of 75 years are given by cause for men and women. CHD was the cause of 15% and 10% of all premature deaths in men and women, respectively. In other parts of Europe, CHD strikes even more: in Europe as a whole, CHD causes 20% of all male deaths before the age of 75 years and 18% of all female deaths before the same age.

In the economically active work force of Europe (ie, those below the age of 65 years), CHD was found to be the cause of death in 16% and 12% of men and women, respectively. Age-standardized and gender-specific CHD mortality rates have significantly decreased during recent decades in many countries in the north, west, and south of Europe. However, the decline has been less apparent, or indeed absent, in Central and Eastern Europe. So based on the mortality statistics, one may conclude that the epidemic of CHD in Europe has been extremely diverse in pattern, magnitude, and timing. The decreases in the standardized CHD mortality rates are the result of great efforts made in preventive cardiology, but there are limitations: in fact, the crude CHD mortality rates remain stable or are even on the increase because of aging of the population. Therefore the total CHD burden remains high, and it may appear paradoxical that as a result of prevention, the total number of CHD deaths could even increase. New therapeutic options for prevention and treatment of CVD have resulted in an increasing number of patients who survive a cardiovascular event; in developed countries, the burden has shifted from the middle aged to the elderly, and the prevalence of CVD increases exponentially with age.

Figure 1. Causes of death in the European Union in males and females under the age of 75 years.

Data from the latest available year. CHD, coronary heart disease; CVD, cardiovascular disease. Based on data from reference 15.

Morbidity
At present there is no standardized source of worldwide or Europe-wide coronary artery disease (CAD) morbidity data. Hospital discharge data can be used, but this provides only part of the picture and the validity of such data in some countries is open to question. The results from the multinational MONItoring of trends and determinants in CArdiovascular disease (MONICA) project are still the best available source of information, although they are now more than 15 years old. Some MONICA centers have continued their registers and have reported more recent results.

The cross-sectional data from MONICA revealed age-standardized annual event rates for fatal and nonfatal coronary events in men aged 35 to 64 years covering a 12-fold range; from 915 per 100,000 for North Karelia, Finland to 76 per 100,000 for Beijing, China. For women, rates covered an 8.5-fold range, from 256 per 100,000 for Glasgow, UK to 30 per 100,000 for Catalonia, Spain.
Twenty-eight-day case fatality rates ranged in men from 37% to 81% and in women from 31% to 91%. From 1985 to 1990, overall 28-day case fatality was halved for hospitalized events (compared with all events), and was nearly halved for hospitalized 24-hour survivors. Because approximately two-thirds of 28-day CHD deaths occurred before individuals reached the hospital, opportunities for reducing case fatalities through improved in-hospital care are limited.

Over the decade studied, CHD mortality rates as defined by MONICA criteria fell annually by an average 2.7% in men (range –8.0% to +4.2%) and by an average 2.1% in women (range –8.5% to +4.1%). Changes in nonfatal rates were smaller (–2.1%; range –6.5% to +2.8%).19 There were, however, important regional differences in all of these changes; countries from the same geographical area have experienced very different time trends in terms of the CHD epidemic. For example, incidence rates for men living in North Karelia, Finland, fell by 6.5% per year from 1983 to 1996, but rose by 1.2% per year for men of the same age living in Kaunas, Lithuania. For women, the incidence fell by 5.1% per year in North Karelia, but rose by 2.7% per year in Kaunas in women of similar age.17

MONICA was partly established to investigate how much of the reported decline in CHD mortality is attributable to improvements in case fatality, and how much is attributable to declines in CHD incidence. The project concluded that, “contribution to changing CHD mortality varied, but in populations in which mortality decreased, coronary event rates contributed two thirds and case fatality one third.”17

Patterns of CHD incidence and case fatality across Europe may have changed since the mid 1990s. Some MONICA centers have been able to continue their registers until now, but in comparing time trends over a longer time period, one has to consider possible differences in the definition of coronary events following the introduction of troponin estimations. In Ghent, Belgium, the register continued, and the MONICA methodology to identify and define acute coronary events was kept identical. In Figure 2, results are given from the register of acute myocardial infarction in the population aged less than 70 years in the city of Ghent. Attack rates are presented for the male population: when comparing the period 1983-1986 with the period 1996-2001, a decline of almost 40% was observed.

In Figure 3, the most recent results from the register up to 2005 are given; since 1999, the study population has been extended up to the age of 74 years. In the figure, attack rates are given for the male and female populations; results are given both for all events and only nonfatal events, the latter meaning only those patients who survived for at least 28 days. The curves have now become very flat; statistically there was no change observed from 1999 to 2005.

This confirms results published from the US, where age-specific mortality rates for CHD have been found to be leveling off in younger adults.11 These observations are also consistent with results from a population-based autopsy study of non-natural deaths, suggesting that temporal declines in the grade of CHD at autopsy have ended.20 All this necessitates continuous and careful monitoring of an epidemic that continues to change over relatively short time periods—indicating the importance of environmental influences—with the use of valid and comparable methods that allow accurate surveillance of the epidemic dynamics.

**Quality of life**

CHD is not only the leading cause of death, but is also an important source of disability that translates into DALYs. In 2002, CHD was the cause of 11% of all DALYs in Europe, comparable to that caused by all cancers. All CVD taken to-
gether was, however, responsible for 23% of all DALYs, and was thus the most important cause.\textsuperscript{15} CVD is responsible for 10% of DALYs lost in low and middle income countries, and 18% in high income countries. The CHD burden is projected to rise from around 47 million DALYs globally in 1990 to 82 million DALYs in 2020.\textsuperscript{1}

The burden of coronary heart disease at the national level

Looking solely at the burden of CHD at the international level may hide important regional differences. In 2005, male life expectancy at the age of 50 years in the 25 countries of the EU varied from 21.3 years in Latvia to 30.4 years in Italy\textsuperscript{16}; for women, the variation between countries was 6.1 years. The healthy life expectancy (HLY) varied even more: the range in HLY at age 50 years was 14.5 years in men and 13.7 years in women. Death rates from CAD are generally higher in Central and Eastern Europe than in Northern, Western, and Southern Europe. For example, the death rate for men aged less than 65 years living in Ukraine is 14 times higher than in France, and for women it is 25 times higher. Likewise, Western Europe has generally higher death rates than Southern Europe: for example, in Ireland, the death rate for men aged less than 65 years is 1.6 times higher than in Italy, and for women it is 1.8 times higher. In Figure 4, the age-standardized mortality rates for CHD in the year 2000 are given for populations aged 45 to 74 years in different European countries; the figures vary from 0.65 to 4.61 per 1000, illustrating that there is still a clear North-East to South-West gradient in CHD mortality within Europe.\textsuperscript{21}

The Institut des Sciences de la Santé carried out a study examining CHD mortality changes in the EU population in individuals less than 75 years of age between 1990/91 and 2000/02. Age-standardized CHD mortality fell in all countries, but not equally across the EU. CHD mortality declined by almost a half in the Czech Republic, the UK, Ireland, and Finland. Elsewhere, rates fell by about one fifth to one third; the only exceptions were Latvian men and Polish women, in whom the improvements were just over 10%.\textsuperscript{22}

But even within countries, significant regional variation in CHD mortality has been observed. In Germany, for example, there was found to be an East-West gradient, with a twofold increased risk of dying from CHD in the state with the highest mortality rate compared with the lowest mortality.\textsuperscript{23} In Great Britain, a North-South gradient has been observed, with CHD mortality rates being higher in the north.\textsuperscript{24} In France, the mortality from CHD also shows a North-South gradient, with very low figures in the south-west region.\textsuperscript{25} In Belgium, large differences in CHD incidence and mortality have been observed, with higher rates in Wallonia compared with Flanders.\textsuperscript{26} All these regional differences are partly explained by variations in classical risk factors and in socioeconomic factors.

Conclusion

The burden of CHD remains high across Europe and the rest of the world. CHD continues to be the main cause of death and a major cause of morbidity and loss of quality of life. The decline in age-standardized mortality rates and in the incidence of CHD in many countries illustrates the potential for prevention of premature deaths and for prolonging healthy life expectancy. However, one should realize that this will paradoxically increase the prevalence of patients with CHD, especially in old age. This is a challenge for modern cardiology; specific attention needs to be given to the development of guidelines in elderly patients. For policy makers, it is also important to know whether major contributors to morbidity and mortality such as CHD are tracking up or down. A valid and actual description of the epidemic by place, by time, and by personal characteristics is continuously needed to guide and support appropriate health policies.
NEW INSIGHTS INTO INITIATION: FROM ISCHEMIA PREVENTION TO IMPROVEMENT IN CORONARY OUTCOMES

References

Keywords: coronary heart disease; epidemiology; prevention; mortality; time trend

LA CHARGE GLOBALE DE LA MALADIE CORONARIE

L’épidémie de maladie coronaire (MC) s’est largement répandue au siècle dernier, ses caractéristiques dans les différentes régions du monde varient nettement, à la fois dans des pays voisins et même entre les régions d’un même pays. Aux États-Unis et dans la plupart des pays de l’Union Européenne, les taux de mortalité par MC ont diminué au cours de l’âge ont diminué de façon significative ; ce qui peut conduire de façon paradoxale à une augmentation de la prévalence de MC dans ces pays ; évidemment, la meilleure survie des patients coronariens et les modifications démographiques se traduisent par une augmentation du nombre de sujets âgés qui souffrent de MC. Dans d’autres parties du monde, l’incidence de MC augmente encore, et l’estimation du nombre de patients coronariens pour les prochaines années est à la hausse, en particulier dans les pays en voie de développement. Le développement récent de l’épidémie aux États-Unis et en Europe suggère de plus que la diminution spectaculaire de la MC dans la dernière moitié du XXe siècle doit être stoppée, surtout chez les plus jeunes. La MC est aussi une importante source de handicap, qui peut se traduire en DALY (années de vie ajustées pour incapacité). Il est également prévu que la charge de la MC en termes de DALY doy augmenter dans les années futures, surtout dans les pays en voie de développement. Le poids de la MC dans chaque pays diffère de façon importante selon les régions. Lorsque ces différences sont bien comprises, on peut en tirer les conséquences et ainsi réduire le fardeau dans les pays les moins favorisés.
Resting heart rate has been directly related to all-cause mortality, cardiovascular mortality, and development of cardiovascular disease in the general population, hypertensive patients, and patients with CAD. Furthermore, emerging data support the addition of heart rate to the list of risk factors for CAD, potentially importantly altering management strategies for patients with CAD.

Several clinical/biological “markers” can aid in detection of patients likely to develop clinical evidence of coronary artery disease and its major sequelae. These may also help guide efforts directed at prevention of cardiovascular events. Heart rate is a well-known risk marker in patients with coronary artery disease, and it is an important component in the generation of ischemia in such patients. Experimental data and clinical observations support a role for heart rate in the pathophysiology of atherosclerosis and plaque rupture. A growing body of evidence points to high resting heart rate as being more than simply a risk marker, but in fact, a risk factor, for adverse outcomes in various populations including those with coronary disease, as heart rate reduction now seems to beneficially alter certain outcomes. The relationship between resting heart rate and cardiovascular mortality is strong, graded, and independent of other factors such as blood pressure and physical activity. The results of the recent BEAUTIFUL (morBidity-mortality EvalUation of the I inhibitor ivabradine in patients with coronary disease and left ventricUlar dysfunction) study underline the importance of heart rate reduction in managing stable coronary disease. Prospective analysis of data from the placebo arm of this study demonstrated that a resting heart rate of ≥70 bpm is a strong independent predictor of clinical outcome. Consistent with these data, ivabradine significantly improved coronary outcomes in patients with a heart rate of ≥70 bpm. Thus, emerging data suggest that heart rate has joined the list of risk factors for coronary artery disease, importantly altering management strategies for affected patients. Heart rate has already appeared in European guidelines for the prevention of cardiovascular events, and should seriously be considered in future guidance documents for patients with coronary artery disease.

Address for correspondence: Professor Jeffrey S. Borer, MD, 47 East 88th Street, New York, NY 10128-1152, USA (e-mail: canadad45@aol.com) www.medicographia.com

Heart rate: from risk marker to risk factor in coronary artery disease

by J. S. Borer, USA

Coronary artery disease (CAD) is a highly prevalent condition and has potentially life-threatening consequences. It affects a large proportion of the general population over the age of 60 years, and according to the Framingham Heart Study, the lifetime risk of developing CAD in individuals aged 40 years is 48% in men and 31% in women. CAD thus represents an important public health problem that is both costly for society and responsible for relatively high mortality and morbidity levels in affected patients. Therefore, there is a clear medical need for guidance on efforts directed at preventing disease progression and associated clinical sequelae. Much of our current understanding of risk markers that identify those like-
Heart rate: from risk marker to risk factor in coronary artery disease – Borer

New insights into isf inhibition: from ischemia prevention to improvement in coronary outcomes

Table. Epidemiological studies on the relationship between heart rate and cardiovascular mortality in the general and hypertensive populations. Abbreviations: AMI, acute myocardial infarction; bpm, beats per minute; HTN, hypertension; IHD, ischemic heart disease; M, men; NS, nonsignificant; SD, standard deviation; W, women.

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Population</th>
<th>Follow-up</th>
<th>CV mortality relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chicago Gas Company ’80</td>
<td>1233 M</td>
<td>15 y</td>
<td>&gt;94 vs &lt;60 bpm: 2.3</td>
</tr>
<tr>
<td>Chicago Heart Ass Project ’80</td>
<td>33,781 M&amp;W</td>
<td>22 y</td>
<td>&gt;90 vs &lt;70 bpm: M: 1.6 W: 1.1 (ns)</td>
</tr>
<tr>
<td>Framingham ’93</td>
<td>45,300 M&amp;W HTN</td>
<td>36 y</td>
<td>&gt;100 vs &lt;60 bpm: M: 1.5 W: 1.4 (ns)</td>
</tr>
<tr>
<td>British Regional Heart ’93</td>
<td>7,735 M</td>
<td>8 y</td>
<td>&gt;90 vs &lt;90 bpm: IHD death 3.3</td>
</tr>
<tr>
<td>Spandau ’97</td>
<td>4,756 M&amp;W</td>
<td>12 y</td>
<td>Sudden death: 5.2 per 20 bpm</td>
</tr>
<tr>
<td>Benetos ’99</td>
<td>19,366 M&amp;W</td>
<td>18.2 y</td>
<td>&gt;100 vs &lt;60 bpm: M: 2.2 W: 1.1 (ns)</td>
</tr>
<tr>
<td>Castel ’99</td>
<td>19,38 M&amp;W</td>
<td>12 y</td>
<td>5th vs 3rd quintile: M: 1.6 W: 1.1</td>
</tr>
<tr>
<td>Cordis ’00</td>
<td>3,257 M</td>
<td>8 y</td>
<td>&gt;90 vs &lt;70 bpm: 2.0</td>
</tr>
<tr>
<td>Reunanen ’00</td>
<td>10,717 M&amp;W</td>
<td>23 y</td>
<td>&gt;84 vs &lt;60 bpm M: 1.4; &gt;94 vs &lt;66 bpm W: 1.5</td>
</tr>
<tr>
<td>Thomas ’01</td>
<td>60,343 M MTN</td>
<td>14 y</td>
<td>&gt;80 vs &lt;80 bpm: &lt;55y: 1.5; &gt;55y: 1.3</td>
</tr>
<tr>
<td>Matis ‘01</td>
<td>2,553 M</td>
<td>9 y</td>
<td>&gt;90 vs &lt;60 bpm: 2.7; 1.5 per 20 bpm</td>
</tr>
<tr>
<td>Ohashama ’04</td>
<td>1,780 M&amp;W</td>
<td>10 y</td>
<td>M: 1.2 W: 1.1 (ns) per 5 bpm</td>
</tr>
<tr>
<td>Okamura ’04</td>
<td>8,800 M&amp;W</td>
<td>16.6 y</td>
<td>M: 1.3 W: 1.2 per 11 bpm (1 SD)</td>
</tr>
<tr>
<td>Jouven ’05</td>
<td>5,713 M</td>
<td>23 y</td>
<td>Sudden death from AMI 3.02 (&gt;75 bpm)</td>
</tr>
</tbody>
</table>

Demonstrating the risk modulation also accounts for possible confounding factors. For example, systemic arterial hypertension is well established as a risk factor for CAD and its sequelae, and also for stroke, not only because it identifies patients at risk for cardiovascular events, but because many studies with many different agents have demonstrated that in hypertensive individuals, risk is reduced when blood pressure is reduced.3 The demonstration of the benefits of blood pressure reduction with many different agents is important: some antihypertensives, including the angiotensin-converting enzyme inhibitors ramipril and perindopril, reduce events through pharmacological effects that appear to be in addition to the benefits of the antihypertensive action itself.5,6 Several criteria have been developed in order to allow one to validate a risk marker as a risk factor, and these are detailed later in this article.

Resting heart rate and prognosis in the general population

Several epidemiological studies support the predictive value of resting heart rate regarding total and cardiovascular mortality (Table).3 The Chicago Peoples Gas Company Study (including 1233 men followed for 15 years), the Chicago Western Electric Company Study (including 1899 men followed for 17 years), and the Chicago Heart Association Detection Project (including 5784 men followed for 5 years), reported together in 1980, were among the earliest studies to demonstrate the prognostic importance of resting heart rate for all-cause mortality in large populations.3 Indeed, multivariate analysis using age, blood pressure, total blood cholesterol, smoking, and body weight as covariates, found heart rate to be an independent predictor both of sudden cardiac death and of noncardiovascular mortality in 2 out of the 3 cohorts studied. A 30-year follow-up of the Framingham study, reported in 1987, demonstrated a significant relationship between heart rate, cardiovascular mortality, coronary heart dis-

Selected abbreviations and acronyms

AMI: acute myocardial infarction
BEAUTIFUL: morBidity morTality EvAuLaTion of the isf inhibitor
CAD: coronary artery disease
GISSI-2: Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto miocardico–2
INVEST: inNational VErapamil SR/trandolapril STudy
MATISS: Malattie Ateriovascolari Aterosclerotiche, Istituto Superiore di Sanità (project)
ease, and sudden coronary death in both men and women. Parallel to these findings, a study of 19,986 "white collar" employees in France followed over a period of 20 years found that resting heart rate was a significant predictor of noncardiovascular mortality in both men and women. In men, the risk of cardiovascular death was lowest among those patients with a heart rate of 60-80 bpm, 81-100 bpm, and >100 bpm were 1.35, 1.44, and 2.18, respectively (all statistically significant). Cardiovascular deaths were primarily and predominantly due to coronary events, and not to cerebrovascular accidents. In men, the predictive value of heart rate was independent of age, hypertension, total cholesterol, body mass index, smoking status, and exercise activity. In women, heart rate did not influence cardiovascular mortality.

Parallel results were reported from the MATISS Project (Malattie cardiovascolari tlerosclerotiche, Istituto Superiore di Sanità), which included 2533 men aged 40 to 69 years. With 24,457 subject-years of follow-up, heart rate was found to independently predict total mortality, cardiovascular mortality, and noncardiovascular mortality. In another French cohort study that included 57,135 asymptomatic apparently healthy working men aged between 42 and 53 years at study entry, a 23-year follow-up demonstrated a significant association between resting heart rate and both sudden and myocardial infarction-related death. The study found that compared with a resting heart rate of <60 bpm, a resting heart rate of >75 bpm defined a relative risk of 3.92 for sudden death. A recently published study undertaken in a French population of 5,139 healthy men found that resting heart rate and the change in resting heart rate over 5 years were both predictors of death, independent of the conventional risk factors. After adjustments were made for confounding factors including baseline heart rate at rest, and results were compared with subjects with an unchanged heart rate, those whose heart rate decreased during the 5 years had a 14% lower mortality risk (P=0.05), whereas men whose heart rate increased over the 5 years had a 19% higher mortality risk (P<0.012).

Resting heart rate and prognosis in patients with coronary artery disease

Hjalmarson et al demonstrated that in patients with acute myocardial infarction (AMI), inhospital mortality and post-discharge mortality increased with increasing heart rate on admission. Total mortality was 15% for patients whose heart rate on admission ranged between 50 and 60 bpm, 41% for those with a heart rate of >90 bpm, and 48% for a heart rate of ≥110 bpm. Mortality after hospital discharge up to 1 year was also related to the maximal heart rate observed in the coronary care unit and heart rate at discharge. The prognostic significance of heart rate was also assessed in 8915 patients with AMI in GISSI-2 (Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto miocardico-2), who were treated with fibrinolytic therapy. Increased heart rate on admission was associated with a progressive increase in hospital mortality (from 7.1% for a heart rate of <60 bpm to 23.4% for a heart rate >100 bpm). In addition, a progressive increase in 6-month mortality was noted with increasing heart rate at discharge (from 0.8% for a heart rate <60 bpm to 14.3% for a heart rate >100 bpm).

Tardif and colleagues investigated 24,913 men and women with suspected or proven CAD who were followed for an average of 14.1 years, and found that resting heart rate was an independent risk marker for total and cardiovascular mortality. The prognostic value of heart rate persisted when analysis was adjusted for hypertension, diabetes, and smoking status, as well as for left ventricular ejection fraction and the number of diseased coronary vessels. Patients with a heart rate ≥83 bpm also had a significantly higher risk of hospital admission for cardiovascular causes than those with a heart rate ≤62 bpm (Figure 1).

In the INternational VErapamil SR/trandolapril STudy (INVEST), the relationship between resting heart rate at baseline and follow-up and adverse outcomes (all-cause death, nonfatal myocardial infarction, and nonfatal stroke) was evaluated in 22,192 patients with hypertension and CAD treated either with verapamil or with atenolol. Resting heart rate was found to be directly associated with adverse events, and heart rate on receiving treatment was even more predictive than baseline heart rate, consistent with the concept that heart rate is a risk factor.

The BEAUTIFUL (morBidity mortality EvAlUaTion of the I inhibition) ivabradine in patients with coronary disease and left ventricULar dysfunction) investigators have added substanc-
New insights into \( \beta \)-inhibition: from ischemia prevention to improvement in coronary outcomes


The BEAUTIFUL placebo data were also analyzed regarding the effect of incremental increases in resting heart rate on cardiovascular outcomes. In fact, for all outcomes, the risk increased with heart rate values >65 bpm. For ischemia-related outcomes (fatal and nonfatal myocardial infarction, revascularization, etc.), risk tended to plateau as heart rate exceeded 70 bpm. By contrast, for heart failure, events continued to increase as heart rate rose. In another analysis in which baseline heart rate was treated as a continuous variable, there were substantial increases in risk with every 5-bpm heart rate incremental increase, and these were highly significant for both hospitalization for heart failure (16%; HR, 1.16; 95% CI, 1.11–1.21; \( P=0.0001 \)) and cardiovascular death (8%; HR, 1.08; 95% CI, 1.03–1.12; \( P=0.0005 \)). Though less striking, each 5-bpm increase in heart rate was also associated with an 8% increase in the likelihood of coronary revascularization (HR, 1.08; 95% CI, 1.01–1.16; \( P=0.034 \)) and a 7% increase in fatal and nonfatal myocardial infarction (HR, 1.07; 95% CI, 1.00–1.14; \( P=0.052 \)).

BEAUTIFUL provides the first prospective assessment of the association between resting heart rate and cardiovascular outcomes in patients with stable CAD. The results lend credence to the results of previous studies in the general population and in normotensive and hypertensive CAD patients.9,17,18 This study is also the first clear demonstration that a relatively high resting heart rate places patients at risk for coronary events, even if they are apparently well treated (including with \( \beta \)-blockade) according to current guidelines. Indeed, the majority of subjects in BEAUTIFUL received concomitant \( \beta \)-blocker therapy—87% of patients in the placebo arm received \( \beta \)-blockers, which is a considerably higher percentage than that observed in population surveys in patients with stable CAD. Thus, the results from the placebo arm of BEAUTIFUL underline the potential value of addressing—and reducing—a resting heart rate of ≥70 bpm in patients with stable CAD.

Role of heart rate in the development of atherosclerosis and coronary events

The most common coronary manifestations of atherosclerosis are stable angina pectoris and acute coronary syndromes. The role of heart rate in the development of myocardial ischemia in patients with stable angina or those suffering from AMI is well known (Figure 3). Increasing heart rate contributes to an imbalance between myocardial oxygen demand and supply, causing both an increase in myocardial oxygen demand and a decrease in coronary blood supply (the latter primarily via a reduction in the duration of diastole, the period during which most myocardial perfusion occurs). Thus, the risk of finding objective evidence of development of myocardial ischemia is related to baseline resting heart rate, with the
Heart rate: from risk marker to risk factor in coronary artery disease – Borer

Criteria for validating heart rate as a risk factor

Several criteria are used to assess the validity of epidemiologic associations in CAD.23,24 Plausibility, based on our current understanding of pathophysiology, provides a basis for concluding that a relation is consistent with the associated disease—CAD in this case. Strength is determined by the relative risk of developing an outcome with the factor versus the risk without. Graduation of effect, analogous to a dose-response curve in pharmacology, is defined by the quantitative impact of a change in the magnitude of the factor or the duration of exposure to the factor versus the outcome of interest. The clearer the graduation of effect, the more likely the factor is indeed a beneficially modifiable risk factor. Consistency is the demonstration of an association between the factor and outcome in a variety of populations, for example, cohorts involving various age groups, both sexes, and different ethnic groups. Perhaps most importantly, if the factor is modifiable with currently available strategies, a diminution of the factor should beneficially modify the outcome. In theory, heart rate reduction should reduce mortality, particularly cardiovascular mortality, in patients with CAD, and most especially, those suffering from AMI. Consistent with this hypothesis, in a review of β-blocker trials on AMI, Kjekshus et al25 observed a relationship between reduction in resting heart rate and a reduction in mortality. Furthermore, a recent meta-regression of randomized clinical trials of β-blockers and calcium channel blockers post-AMI strongly suggested that the beneficial effects of these agents are proportionally related to the reduction in resting heart rate.26 A statistically significant relationship was found between reduction in resting heart rate and decreases in cardiac death, all-cause death, sudden death, and recurrence of nonfatal myocardial infarction. This meta-regression suggests that reduction of resting heart rate could be a major determinant of the clinical benefits seen in these trials. This hypothesis was also tested more recently in randomized controlled trials of β-blockers in heart failure caused by left ventricular systolic dysfunction. There was a close relationship

Figure 3. Role of heart rate in the pathophysiology of coronary artery disease. CV, cardiovascular.

Figure 4. Treatment with ivabradine reduces the risk of coronary outcomes in patients with stable coronary artery disease and left ventricular systolic dysfunction with a resting heart rate ≥70 beats per minute. RRR, relative risk reduction.

between the all-cause annualized mortality rate and heart rate in these studies, and a strong correlation between change in heart rate and change in left ventricular ejection fraction. However, β-blockers not only reduce heart rate, but also have several other cardiovascular effects. The novel specific heart rate-lowering agent, ivabradine, therefore provides an opportunity to assess the effects of lowering heart rate without directly altering other aspects of cardiovascular function. In this context, the BEAUTIFUL results have added substantially to our understanding of the role of heart rate reduction in the prevention of coronary events, as reviewed above. In patients with stable CAD and left ventricular systolic dysfunction who had an elevated heart rate, >70 bpm, ivabradine reduced the relative risk of hospitalization for fatal and nonfatal AMI by 36% (P=0.001) and reduced coronary revascularization by 30% (P=0.016) (Figure 4, page 353). Treatment with ivabradine was also associated with a 22% reduction in the relative risk of a composite end point of hospitalization for fatal and nonfatal AMI and unstable angina pectoris (P=0.023) compared with placebo. These data suggest that heart rate is a risk factor for CAD, and that its reduction may decrease coronary events in this population. Heart rate has already appeared in European guidelines regarding the prevention of cardiovascular events, and should be seriously considered in future guidance documents relating to patients with CAD.

**Conclusion**

Resting heart rate has been directly related to all-cause mortality, cardiovascular mortality, and development of clinically evident cardiovascular disease in the general population, hypertensive patients, and patients with CAD. These data emphasize the importance of heart rate as a cardiovascular risk factor, particularly among patients with CAD. As a result, heart rate should be measured routinely in daily clinical practice. The results of BEAUTIFUL suggest that treatment with ivabradine in patients with ischemic heart disease and a heart rate ≥70 bpm may reduce coronary outcomes. Thus, emerging data support the addition of heart rate to the list of risk factors for CAD, potentially importantly altering management strategies for patients with CAD.

**References**

27. Flannery G, Gehrig-Mills R, Billah B, et al. Analysis of randomized controlled trials on the effect of magnitude of heart rate reduction on clinical outcomes with ivabradine in patients with ischemic heart disease and a heart rate ≥70 bpm may reduce coronary outcomes. Thus, emerging data support the addition of heart rate to the list of risk factors for CAD, potentially importantly altering management strategies for patients with CAD.

**Keywords:** coronary artery disease; cardiovascular event; heart rate; risk marker; risk factor
Pour aider la détection des patients à risque, ce qui peut aussi favoriser les efforts de prévention cardio-vasculaire, il existe un certain nombre de marqueurs (biologiques et cliniques) de risque de développement de la maladie coronaire et des séquelles majeures. La fréquence cardiaque, marqueur de risque bien connu pour les patients coronariens, est un facteur important dans l’installation de l’ischémie chez ces patients. Le rôle de la fréquence cardiaque dans la physiopathologie de l’athérosclérose et la rupture de la plaque est conforté par des données expérimentales et des observations cliniques. De plus en plus d’arguments croissants laissent penser qu’une fréquence cardiaque de repos élevée représente plus qu’un simple marqueur de risque, mais bien un facteur de risque d’événements indésirables pour des populations variées, comme les patients coronariens. Une réduction de la fréquence cardiaque semble modifier positivement certains de ces événements. Les relations entre la fréquence cardiaque de repos et la mortalité cardio-vasculaire sont fortes, graduées et indépendantes d’autres facteurs comme la pression artérielle et l’activité physique. Les résultats de la récente étude BEAUTIFUL (morBidity-mortality EvAlUaTion of the I\textsubscript{i} inhibitor ivabradine in patients with coronary disease and left ventricULar dysfunction) soulignent l’importance de la réduction de la fréquence cardiaque dans la prise en charge de la maladie coronaire stable. Une analyse prospective des données du bras placebo de cette étude a démontré qu’une fréquence cardiaque de repos de ≥ 70 battements par minute (bpm) est un important facteur prédictif indépendant d’événements cliniques. En accord avec ces données, l’ivabradine a amélioré de façon significative les événements coronaires des patients dont la fréquence cardiaque était ≥ à 70 bpm. Ces données laissent donc penser que la fréquence cardiaque a rejoint la liste des facteurs de risque de maladie coronaire, en modifiant de façon importante la stratégie de la prise en charge des patients atteints. La fréquence cardiaque est déjà mentionnée dans les recommandations européennes pour la prévention des événements cardio-vasculaires et devrait être sérieusement prise en compte dans les futurs recommandations délivrées aux patients coronariens.
A high heart rate is associated with an elevated mortality rate both in the general population as well as populations with hypertension or established cardiovascular disease like coronary artery disease (CAD) and heart failure. In view of this epidemiological background, it has been suggested that pharmacological heart rate reduction might improve cardiovascular complications. This pharmacological approach became available after the development of the $I_f$ channel inhibitor ivabradine. Ivabradine reduces heart rate by depressing the phase of spontaneous depolarization of the sinus node. The sinus node activity of the drug is specific, and therefore no cardiodepressant effects on atrioventricular conduction or inotropy are induced. In experimental models of atherosclerosis, ivabradine was able to reduce endothelial dysfunction and inhibit plaque formation. In the large outcome trial, BEAUTIFUL (morBidity-mortality EvAlUaTion of the $I_f$ inhibitor ivabradine in patients with coronary disease and left ventricULar dysfunc-tion), ivabradine was able to reduce ischemia-related outcomes like reinfarc-tion or the necessity for coronary revascularization in patients with known CAD after myocardial infarction. Furthermore, ivabradine has an established role in the symptomatic treatment of CAD and angina syndromes to reduce myocardial ischemia—alone, and even in the presence of β-blockers. A trial of ivabradine in chronic heart failure, the end stage of CAD, is currently being performed (Systolic Heart failure treatment with the $I_f$ inhibitor ivabra-dine Trial; SHIFT). The data of this large outcome trial will establish whether the beneficial effects in experimental models might translate into a reduction of hard clinical end points in clinical practice in patients with advanced CAD or heart failure.

Heart rate is highly variable, and acts as the predominant driving force for cardiovascular regulation in mammals, including humans. Heart rate contributes closely to myocardial work and energy requirements, thus influencing the balance of cardiac performance and economy. It seems plausible that, via myocardial mechanical and metabolic stimulation, heart rate could impose stress on the myocardium and may therefore play an important role in determining life expectancy as well as lifespan in all individuals. This biological background is supported by many studies and investigations. The myocardium with compromised function shows a significant rightward shift of the normal physiological pressure-volume curves (Figure 1). The external work is greatly decreased, whereas much
more internal energy is generated, which consequently decreases efficiency.\textsuperscript{2,3} These energy considerations are in line with the specific interrelation between heart rate and life expectancy (Figure 2). It is striking that mammals with the highest heart rates at rest have the shortest lifespan. The opposite holds true for those mammals with the lowest heart rates (Figure 2). Lowering heart rate reduces the ischemic threshold of diseased hearts, reduces heart work, and thus might be a potential therapeutic target of treatment in heart disease. According to detailed calculations, heart rate reduction of 10 beats per minute (bpm) can save about 5 kg of adenosine triphosphate per lifetime in humans.\textsuperscript{4}

An increase in sympathetic activity and a decrease in parasympathetic activity increases heart rate. Stimulation of the sympathetic nervous system can cause myocordial apoptosis as well as sudden cardiac death.\textsuperscript{5,6} Consequently, it is difficult to distinguish between the influence on life expectancy of increased heart rate itself (metabolic demand), and the potential imbalance between sympathetic and parasympathetic neuroendocrine regulation. Experimentally, the pharmacological reduction of heart rate with cardiac glycosides like digitalis has been found to cause a 30% prolongation of survival time in healthy mice (Figure 3, page 358).\textsuperscript{7} This may support the notion that reduction of heart rate could itself prolong survival time in mammals, at least in part independently of the activity of the autonomic nervous system. The open question is whether these effects of heart rate modulation primarily act on the vessels or on the myocardium.
Heart rate and survival in healthy and hypertensive individuals

Epidemiological studies investigating approximately 30,000 individuals in total over a time period of between 5 and 36 years have revealed an inverse relationship between heart rate and survival time. The risk for total mortality, coronary artery disease (CAD), stroke, and death caused by noncardiovascular diseases significantly increased in an age- and gender-independent manner with higher heart rates (Figure 4). According to the Cardiovascular Study in the Elderly (CASTEL), this relationship is especially true for patients older than 65 years. In clinical practice, it can be assumed that high heart rate is correlated with an increase in mortality caused by CAD, and is associated with an increased risk of sudden cardiac death. Maximal heart rate developed during exercise, the difference between this heart rate value and the resting heart rate, and the time course of the heart rate returning to normal values after exercise are risk factors for sudden cardiac death if abnormal. Compared with resting heart rates of about 60 to 65 bpm, resting heart rates of about 88 to 99 bpm are associated with a five- to sixfold increase in the risk of sudden cardiac death in men and a twofold increase in women. The total mortality rate doubles with a rise in heart rate of about 40 bpm. This correlation is strengthened when further risk factors like older age, hypertension, diabetes mellitus, and high body mass index are present. The association between heart rate and the development of arterial hypertension was first demonstrated in soldiers after their return from the First World War. Follow-up in these individuals revealed a significant correlation between heart rate and the development of hypertension, cardiovascular disease, and chronic renal failure. These findings were supported by the prospectively designed Hypertension and Ambulatory Recording VEnetia Study (HARVEST), which showed a link between high heart rates and a further increase in blood pressure in stage 1 hypertensive individuals. Additionally, Gillum et al demonstrated that patients with arterial hypertension have higher heart rates compared with healthy individuals. Complications of cardiovascular disease as well as total mortality double as heart rate increases by 40 bpm. Heart rate therefore appears to be associated with vascular risk factors like hypertension.

Atherosclerotic heart disease—heart rate and mechanisms of atherosclerosis

Experimentally, in vitro studies have demonstrated that the stretching of human smooth muscle cells enhances the release of angiotensin II in a frequency-dependent manner and thereby stimulates the production of collagen in the vessel wall. This effect can be antagonized by angiotensin receptor 1 antagonists. Corresponding to this result, the stiffness of the arterial vessel wall rises with increasing heart rates. This close correlation has especially been revealed in individuals suffering from hypertension. The combination of increased blood pressure with repetitive pressure changes caused by higher heart rates imposes an additional mechanical load on the vessel wall, potentially increasing the risk of clots. In monkeys, a strong correlation was shown between an increased hemo-
Dynamic stress index (heart rate multiplied by mean arterial blood pressure) and the development of atherosclerosis in the aorta or iliac vessels.26

Experimental heart rate reduction
Heart rate reduction caused by sinus node ablation in monkeys fed with a cholesterol-rich diet was found to be associated with a decrease in coronary atherosclerotic lesions.28 Additionally, in young patients with myocardial infarction, there is a strong positive relationship between higher heart rates and the extent of atherosclerotic coronary lesions.30 Pharmacological inhibition of heart rate was possible after the development of the If channel inhibitor ivabradine. In ApoE knockout mice, cholesterol-induced atherosclerosis was inhibited by heart rate reduction with ivabradine.31 Heart rate reduction of 10% led to a 40% decline in plaque load of the aortic sinus and a 70% decline in plaque load in the ascending aorta (Figure 5). Mechanistically, a reduction in NADPH (nicotinamide adenine dinucleotide phosphate) oxidase and superoxide production—and thus in oxidative stress—might be involved (Figure 6). In earlier stages of atherosclerosis, a reduction in endothelial dysfunction was observed with heart rate reduction by ivabradine.32 Presumably, therefore, mechanical load on the vessel wall caused by higher heart rates might lead to endothelial dysfunction, increased oxidative stress, and enhanced plaque formation, which can be reversed or prevented by the inhibition of If channels and consecutive heart rate reduction with ivabradine.31,32

Figure 5. Atherosclerotic lesions in the aortic sinus (upper panels) and the ascending aorta (lower panels) in ApoE knockout mice treated with vehicle and ivabradine. The original slices demonstrate a marked reduction in plaque burden.


Figure 6. Panel A: nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity; Panel B: superoxide anion production; Panel C: lipid hydroperoxidase; and Panel D: dehydroetidium (DHE) fluorescent staining, in ApoE KO mice treated with vehicle or ivabradine. Heart rate reduction with ivabradine leads to a marked reduction in NADPH oxidase, superoxide production, lipid peroxidation, and free radicals according to fluorescence measurement with DHE.

Coronary artery disease and myocardial infarction

Events in patients with stable CAD are correlated with resting heart rate.35 Diaz et al investigated 24 913 patients and demonstrated that total mortality rate, the mortality rate for cardiovascular diseases, as well as the rate of cardiovascular rehospitalization increases with increasing heart rate.34 Patients with a resting heart rate of more than 83 bpm had an increased relative risk of 1.23 and an elevated cardiovascular mortality risk of 1.31 compared with the control group. Kaplan et al demonstrated a reduced progression of atherosclerosis in monkeys fed with a cholesterol-rich diet, as a result of heart rate lowering with propranolol.36 A high heart rate could additionally impair the stability of coronary plaques through enhanced mechanical stress caused by repetitive pressure changes. Myocardial infarction develops when coronary plaques rupture and thrombosis occludes the vessel. The probability of plaque rupture depends on the stability of the fibrous cap covering the plaque shoulder, as well as the mechanical stress imposed on it. An increased mechanical load has been shown to provoke rupture of the plaque.37 Furthermore, Lee et al found that rupture of explanted human aortic plaques was augmented with increased heart rates.37 This effect was supported by the work of Heidland man aortic plaques was augmented with increased heart rates.38

Kaplan et al demonstrated a reduced progression of atherosclerosis in monkeys fed with a cholesterol-rich diet, as a result of heart rate lowering with propranolol.36 A high heart rate could additionally impair the stability of coronary plaques through enhanced mechanical stress caused by repetitive pressure changes. Myocardial infarction develops when coronary plaques rupture and thrombosis occludes the vessel. The probability of plaque rupture depends on the stability of the fibrous cap covering the plaque shoulder, as well as the mechanical stress imposed on it. An increased mechanical load has been shown to provoke rupture of the plaque.37 Furthermore, Lee et al found that rupture of explanted human aortic plaques was augmented with increased heart rates.37 This effect was supported by the work of Heidland man aortic plaques was augmented with increased heart rates.38

Accordingly, heart rate–reducing verapamil-like calcium antagonists have beneficial effects in terms of prognosis of patients after myocardial infarction in the absence of heart failure.45 In contrast, dihydropyridine-type calcium antagonists have detrimental effects on survival because of reflex tachycardia.

Taken together, heart rate reduction is correlated with an improvement in the long-term survival of patients with myocardial infarction, which has been best demonstrated by β-blocker trials.

Effects of heart rate reduction on outcome

The role of β-channel inhibition on cardiovascular events in patients with CAD and reduced left ventricular function was studied in BEAUTIFUL (morBidity mortality EvAlUaTion of the β inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction).46-47 The BEAUTIFUL investigators studied patients with known CAD who also presented with left ventricular dysfunction. In the epidemiological part of the trial,47 it was shown that patients had an adverse prognosis if heart rate was above 70 bpm (Figure 8). This held true for hospitalizations for heart failure, coronary revascuularization, and cardiovascular death. Treatment with ivabradine48 resulted in a reduction of ischemia-related end points like myocardial infarction and cardiovascular revascularization in patients with a heart rate above 70 bpm. The combined end point was not significantly affected by the treatment with ivabradine. It thus seems apparent that atherosclerosis, and in particular atherosclerotic events, are favorably influenced by a reduction in heart rate. This is not self-evident, because in a reduced heart rate, other mechanisms like higher daily levels of exercise, fewer comorbidities, and less obesity might be involved.49 Nevertheless, further trials will have to establish the role of β-channel inhibition, possibly in other conditions associated with high heart rates such as heart failure or renal damage in high-risk hypertensive individuals.49,50
Future perspectives: heart failure
As with the conditions hypertension and CAD, heart failure, in particular in the decompensated state, is accompanied by high heart rates. This is brought about by activation of the sympathetic nervous system as one component of neuroendocrine activation. It is also known that in this condition, elevated heart rate is associated with a poor outcome. Heart rate reduction has been discussed as being one of the mechanisms by which $\beta$-blockers mediate an improvement of outcome in heart failure. Interestingly, there is discussion that in heart failure, there may be energy depletion, which is improved by heart rate reduction. Furthermore, in the failing heart, the positive force frequency relationship turns into a negative inverted relationship that results in a decline in the force of contraction when heart rate is increased (impaired Bowditch-effect). It is therefore tempting to speculate that heart rate reduction might also be beneficial to reduce heart failure–related events.

However, in BEAUTIFUL, heart failure hospitalizations were not significantly reduced. It is noteworthy that heart rate in BEAUTIFUL was rather low. It was therefore extremely important to carry out a trial specifically in patients with heart failure and neuroendocrine activation, and therefore higher heart rates. In Systolic Heart failure treatment with the $I_f$ inhibitor ivabradine Trial (SHIFT), patients with heart failure who are...
on standard medication are being investigated. These patients are receiving ivabradine as an add-on therapy. The average heart rate in SHIFT is higher than in BEAUTIFUL.

Therefore, this trial will give a definite answer as to whether there is a reduction in heart failure outcome with heart rate reduction in this high-risk population. Furthermore, it will provide proof of the pathophysiological concept that along the cardiovascular continuum, events are dependent on heart rate and can be targeted by heart rate-lowering therapies (Figure 9). All patients are randomized in SHIFT and the results can be expected at the end of 2010.

**Figure 9.** Clinical and experimental evidence for the potential role of heart rate along the cardiovascular continuum. In patients with high heart rates, there is a high risk of the development of atherosclerosis. A high heart rate leads to ischemia and remodeling of the heart and vessels, and contributes to comorbidities in hypertension and chronic heart failure. Inhibition of the β-channel might reduce heart rate, and therefore cardiovascular events, following treatment with ivabradine.


**Conclusion**

Heart rate is an independent risk factor for patients with cardiovascular disease, in particular arterial hypertension, myocardial infarction, CAD, and heart failure. This relationship is supported by a large number of animal studies that have shown detrimental effects of increased heart rate on the function and structure of the cardiovascular system, in particular in atherosclerosis. Whether pharmacological heart rate reduction might be beneficial in other conditions, such as for prevention of atherosclerotic disease or heart failure, must be the subject of future clinical trials.

**References**

20. Palatini P, Casiglia E, Pauletto P. Relation between physical training and ambulatory blood pressure in stage I hypertensive subjects. Results of the Har-
une fréquence cardiaque élevée est associée à un taux élevé de mortalité à la fois dans la population générale et dans les populations hypertendues ou souffrant de maladie cardiovasculaire établie comme la maladie coronaire (MC) et l’insuffisance cardiaque (IC). Dans ce contexte épidémiologique, une réduction pharmacologique de la fréquence cardiaque pourrait améliorer les complications cardiovasculaires. Cette approche pharmacologique est devenue possible avec le développement de l’ivabradine, inhibiteur du canal If. L’ivabradine ralentit la fréquence cardiaque en inhibant la phase de dépolarisation spontanée du nœud sinusal ; cette action est spécifique et n’entraîne donc aucun effet cardiodépresseur sur la conduction auriculoventriculaire ou sur l’inotropisme. Dans des modèles expérimentaux d’athérosclérose, l’ivabradine diminuait la dysfonction endothéliale et inhibait la formation de la plaque. Dans la grande étude BEAUTIFUL (morbidité mortalité EvAilUAtion of the If inhibitor ivabradine in patients with coronary disease and left ventricular systolic dysfunction (BEAUTIFUL)), un randomized, double-blind, placebo-controlled trial, Lancet. 2008;372:817-821.


Keywords: coronary artery disease; atherosclerosis; heart failure; cardiovascular complication; heart rate; mortality rate; ivabradine.
Is heart rate optimally controlled in patients with coronary artery disease in clinical practice?

by C. Daly, Ireland

Myocardial oxygen demand is primarily controlled by heart rate, which also controls myocardial oxygen supply, and an elevated heart rate can trigger myocardial ischemia. Furthermore, emerging evidence suggests that as an independent cardiovascular risk factor, heart rate may be comparable in importance to smoking, dyslipidemia, or hypertension, yet this is often overlooked. Data on the control of heart rate in clinical practice is scarce, and that which do exist, ie, in registries of acute coronary syndromes and post–myocardial infarction populations, suggest that elevated resting heart rate is common. A resting heart rate of >75 beats per minute, the level above which the risk of cardiac events begins to increase, is found in a substantial proportion of patients post–myocardial infarction—up to one third of women and one quarter of men. Observational data from studies of preoperative β-blockade, and meta-analysis of the effect of preoperative β-blockade on mortality reduction, point to considerable inter-patient variability in heart rate response to β-blockade. There are also indications that a substantial proportion of patients fail to achieve target heart rates (over 25%) and that attainment of target heart rate is necessary to achieve cardio-protection with β-blockade. Data from the Euro Heart Survey of Angina suggest that heart rate control is not optimal in the stable angina setting, despite its proven benefits with regard to reducing ischemia, with multiple factors including comorbidity affecting the use of β-blockers.
The community in recent times. Despite its simplicity, heart rate may have only become more widely realized in the clinical com-


dence is reported. The analogy may be drawn between this and earlier scant reporting of either cholesterol levels or the development is directly related to baseline resting heart rate. Myocardial ischemia was more than twice as likely in patients with a baseline heart rate of $\geq 80$ beats per minute (bpm) rather than $<60$ bpm, and the anti-ischemic activity of each type of medication was related chiefly to each drug’s ability to reduce heart rate.5

A considerable amount of the available data regarding the effect of elevated heart rate on ischemia was published over 15 years ago, and although guidelines for the management of angina emphasize the need to achieve target heart rates to control ischemia,6,9 the significance of raised resting heart rate as a major prognostic indicator and target for treatment has only become more widely realized in the clinical community in recent times.10 Despite its simplicity, heart rate may be comparable in importance as an independent cardiovascular risk factor to smoking, dyslipidemia, or hypertension, yet this is often overlooked.

**Heart rate and prognosis**

There have been several large observational studies showing elevated heart rate to be associated with adverse outcome in both the coronary disease population and the general population.11,12 A key study in this regard showed resting heart rate to be a predictor of total and cardiovascular mortality in nearly 25 000 patients with CAD.13 Patients from the Coronary Artery Surgery Study registry were followed up for a median 14.7 years, and those with a resting heart rate of $\geq 83$ bpm had significantly increased risks of total mortality (hazard ratio [HR] 1.32; $P<0.0001$) and cardiovascular mortality (HR 1.31; $P<0.0001$), after adjustment for other clinical variables.13 In BEAUTIFUL (morBidity-mortality EvAluation of the $I_{1}$ inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction), a large study of CAD pa-
tients with left ventricular systolic dysfunction, patients with a heart rate of $\geq 70$ bpm had a 34% increased risk of cardiovascular death ($P=0.0041$), a 53% higher risk of admission to hospital for heart failure ($P<0.0001$), a 46% greater risk of admission to hospital for myocardial infarction ($P=0.0066$), and a 38% higher risk of coronary revascularization (38%; $P=0.037$).14 The International $V_{E}$Rapamil SR/Trandolapril study (INVEST), which included over 22 000 patients with stable CAD and hypertension randomized to verapamil or atenolol, demonstrated a similar linear increase in the risk of cardiovascular events with increasing resting heart rate, with risk increasing significantly at a heart rate of approximately 75 bpm.15 And the effects of heart rate on outcome are evident across the spectrum of coronary presentations. A recent report on prognostic indicators in a low risk population presenting with acute coronary syndromes (ACS; $n=15,000$) selected heart rate at presentation as an important clinical indicator of the likelihood of freedom from events, with lower heart rates associated with fewer events during follow-up.16

**Treatment of heart rate**

Heart rate reduction has been associated with clinically important benefits in various subtypes of coronary heart dis-
tease.1 Pooled data from 8 randomized, double-blind studies of $\beta$-blockade revealed that during the evolution of myocardial infarction (ie, within 12 hours of symptom onset), a de-
crease in heart rate of $\pm 14$ bpm was linked to a 25% to 30% decrease in infarct size.17 Moreover, in large-scale, pooled analyses of post-infarct patients, a mean heart rate decrease of approximately 10 bpm was associated with reduced risks of approximately 20% to 25% in total mortality, cardiac death, and nonfatal reinfarction.17,18 In specific studies of angina and silent myocardial ischemia prevention, the most marked efficacy has been documented for agents with the most sustained decreases in heart rate.18 The American College of Cardiology and American Heart Association now recommend a target resting heart rate of $\leq 60$ bpm for $\beta$-blocker–treated patients with stable angina.8

**Heart rate lowering in practice**

Despite the proven benefits of heart rate reduction in reduc-
ing ischemia and angina, and the association of lower heart rates with improved prognosis, only relatively limited data exist on the attainment of heart rate targets in clinical prac-
tice or the use of pharmacological therapies to achieve target heart rate. The vast majority of studies on pharmacological therapies or revascularization in CAD populations do not even report resting heart rate at baseline, even when blood pres-
ure is reported. The analogy may be drawn between this and earlier scant reporting of either cholesterol levels or the
use of antilipid or antiplatelet therapies. Resting heart rate and heart rate during follow-up are reported in a handful of studies that have looked at management of ischemia in stable angina, as such as Total Ischaemic Burden European Trial (TIBET), a study using atenolol, and Angina Prognosis Study in Stockholm (APSS), a study using metoprolol, as well as more recent trials such as the aforementioned INVEST and BEAUTIFUL. But accurate data regarding the actual heart rates routinely encountered in “real world” patients are rare.

**Acute coronary syndromes and myocardial infarction**

The Global Registry of Acute Coronary Events (GRACE) was designed to reflect an unbiased population of patients with ACS, irrespective of geographical region. More than 120 hospitals located in 14 countries in North and South America, Europe, Australia, and New Zealand contributed patients who had been admitted with a presumptive diagnosis of ACS (that is, had symptoms consistent with acute ischemia), and had at least one of the following: electrocardiogram (ECG) changes consistent with ACS, serial increases in serum biochemical markers of cardiac necrosis, and documentation of CAD. In this population (n=15,757), the median heart rate (interquartile range) was 76 bpm (65-90 bpm). In those free of events, the median heart rate was 75 bpm (64-88 bpm), and in those who went on to die or develop further myocardial infarction or revascularization, it was 83 bpm (70-100 bpm).

<table>
<thead>
<tr>
<th>Heart rate (bpm)</th>
<th>Male n=9601</th>
<th>Female n=1647</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;59</td>
<td>16</td>
<td>10.3</td>
</tr>
<tr>
<td></td>
<td>0.88 (0.68-1.14)</td>
<td>1.52 (0.71-3.23)</td>
</tr>
<tr>
<td>60-64</td>
<td>22.6</td>
<td>19.7</td>
</tr>
<tr>
<td></td>
<td>0.84 (0.66-1.01)</td>
<td>1.48 (0.52-1.93)</td>
</tr>
<tr>
<td>65-69</td>
<td>14.9</td>
<td>13.4</td>
</tr>
<tr>
<td></td>
<td>1.0</td>
<td>1</td>
</tr>
<tr>
<td>70-74</td>
<td>21.6</td>
<td>23.3</td>
</tr>
<tr>
<td></td>
<td>0.97 (0.71-1.27)</td>
<td>1.48 (0.82-2.67)</td>
</tr>
<tr>
<td>&gt;75</td>
<td>24.9</td>
<td>33.3</td>
</tr>
<tr>
<td></td>
<td>1.32 (1.07-1.63)</td>
<td>1.52 (0.87-2.67)</td>
</tr>
</tbody>
</table>

**Table.** Heart rate and associated risk of mortality in the GISSI-Prevenzione study.

Bpm, beats per minute; CI, confidence interval; RR, relative risk.


In the PURSUIT (Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using IntegriL) registry of ACS, only limited data were presented regarding heart rate at baseline; median heart rate was 72 bpm (63-80 bpm), but heart rate was significantly associated with clinical events during follow-up, with the effect greater for myocardial infarction than for unstable angina (Figure, page 367). The GISSI (Gruppo Italiano per lo Studio della Streptochinasi nell’Infarto miocardico)-Prevenzione study collected data on almost 12,000 patients who had suffered a myocardial infarction in the previous 3 months, and found that a quarter of men and one third of women had a heart rate >75 bpm (Table), which in this study was also associated with an increased risk of subsequent mortality.

Even when published, for the most part, data from registries of ACS and myocardial infarction patients regarding the resting heart rates encountered in clinical practice are relatively limited. In particular, there is limited information regarding the interrelationship between anti-ischemic and chronotropic medications such as β-blockers or calcium antagonists and the measured heart rate, and no published data on the relationship between resting heart rate and comorbid conditions such as chronic respiratory disease, diabetes, or peripheral vascular disease. Even more importantly, there is no data on the influence of heart rate on subsequent management, the effect of pharmacological interventions on follow-up heart rates, or the effect, if any, of successful heart rate modification on mortality or other outcomes. In effect, there is little data on the control of heart rate in clinical practice.

**Perioperative heart rate lowering**

An exception and important data source on this topic is the literature surrounding β-blockade for the prevention of perioperative cardiac events in vascular surgery patients. Patients undergoing vascular surgery have a high risk of suffering major postoperative cardiac events. This risk can be modified by perioperative β-blockade, although there has been debate in recent years as to the universal benefit of β-blockade in such patients.

Preoperative myocardial ischemia as detected by Holter monitoring identifies a high-risk subgroup of patients in whom postoperative ischemia, similarly detected, heralds major cardiac events. In one study, Holter monitoring was used to select patients for β-blockade, and it was shown that systematic, patient-specific postoperative heart rate control with β-adrenergic blocker therapy can decrease the incidence of postoperative ischemia among high-risk vascular surgery patients. A total of 26 of 150 patients due to undergo elective vascular surgery who were monitored preoperatively by 24-hour Holter monitoring were found to have significant myocardial ischemia defined by ST-segment depression. The ischemic threshold was defined as the minimal heart rate at which this ST-segment depression occurred. These 26 patients were then randomized to receive continuous intravenous β-blockade with esmolol or placebo plus usual medical therapy, with the aim of reducing the postoperative heart rate to 20% below the ischemic threshold. All patients were monitored for 48 hours postoperatively. Postoperative Holter readings were analyzed for the incidence of ischemia and for the number of hours during which heart rate was controlled below the ischemic threshold. A total of 15 patients were randomized to receive esmolol, and 11 were randomized to receive placebo. The two groups were comparable with respect to clinical characteristics and incidence.
and duration of preoperative ischemia. Ischemia persisted in the postoperative period in 8 of 11 placebo patients (73%), but only 5 of 15 esmolol patients (33%) (P<0.05). Of the 15 esmolol patients, 9 had mean heart rates below the ischemic threshold, and all 9 patients had no postoperative ischemia. A total of 4 of 11 placebo patients had mean heart rates below the ischemic threshold, and 3 out of the 4 had no postoperative ischemia. There were two postoperative cardiac events among patients who had postoperative ischemia (one placebo, one esmolol) and whose mean heart rates exceeded the ischemic threshold. These data suggest that patient-specific, strict heart rate control aimed at a predefined target based on the individual preoperative ischemic threshold was associated with a significant reduction and frequent elimination of postoperative myocardial ischemia among high-risk patients.

Figure. Data from the PURSUIT (Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using InTegrilin) registry of ACS. There was a significant association between heart rate and clinical events during follow-up, with the effect greater for myocardial infarction (MI) than for unstable angina pectoris (UAP). BPM, beats per minute; CI, confidence interval; OR, odds ratio.

NEW INSIGHTS INTO \( \beta \)-INHIBITION: FROM ISCHEMIA PREVENTION TO IMPROVEMENT IN CORONARY OUTCOMES

In a more recent observational cohort study, 272 vascular surgery patients were preoperatively screened for cardiac risk factors and \( \beta \)-blocker dose, with \( \beta \)-blocker dose expressed as a percentage of the maximum recommended therapeutic dose, and the effect of higher \( \beta \)-blockade and lower heart rate were evaluated.\(^{26}\) \( \beta \)-Blocker dose was converted to a percentage of the maximum recommended therapeutic dose according to the Food and Drug Administration's Center for Drug Evaluation and Research database. The maximum recommended therapeutic dose for atenolol was 3.330 mg/kg (body weight) per day, for bisoprolol it was 0.330 mg/kg (body weight) per day, for metoprolol 6.670 mg/kg (body weight) per day, for carvedilol 0.417 mg/kg (body weight) per day, for propranolol 10.700 mg/kg (body weight) per day, and for labetalol 40.700 mg/kg (body weight) per day. Heart rate and ischemic episodes were recorded by continuous 12-lead electrocardiography, starting 1 day before to 2 days after surgery, and serial troponin T levels were measured after surgery. Of the 272 patients, myocardial ischemia was detected in 85 patients (31%) and troponin T release in 44 patients (16.2%). Higher doses of \( \beta \)-blockers were significantly associated with lower heart rates during 12-lead ECG monitoring (78.8 ±11.8, 73.1 ±11.1, and 68.0 ±10.9 bpm in patients with no dose, low-dose, and high-dose \( \beta \)-blockers, respectively, \( P<0.0001 \)), and nonsignificantly associated with lower absolute heart rate change (11.3 ±8.5, 9.6 ±7.2, and 8.5 ±9.7 bpm in patients with no dose, low-dose, and high-dose \( \beta \)-blockers, respectively, \( P=0.092 \)). In multivariate analysis, higher preoperative heart rates during ECG monitoring (per 10-bpm increase) were significantly associated with an increased incidence of myocardial ischemia (HR, 2.49; 95% CI, 1.79 to 3.48), troponin T release (HR, 1.53; 95% CI, 1.16 to 2.03), and long-term mortality (HR, 1.42; 95% CI, 1.14 to 1.76), with similar patterns observed for intraoperative and postoperative heart rates. This study confirmed that tight heart rate control is associated with reduced perioperative myocardial ischemia, and it further expanded findings by showing that reduced heart rate is also associated with reduced troponin T release and improved long-term outcome in vascular surgery patients.

Following on from such studies, a recent meta-analysis sought to determine the part played by tight heart rate control in the efficacy of perioperative \( \beta \)-blockade. Previous meta-analyses of trials assessing the efficacy of perioperative \( \beta \)-blockade failed to show a consistent reduction in postoperative morbidity and mortality, but showed sizeable heterogeneity of effect, and found that the influence of tight heart rate control had not been considered. The current meta-analysis included 2176 patients from 10 studies, and grouped the trials on the basis of maximal heart rate.\(^{27}\) Trials in which the estimated maximal heart rate was <100 bpm were associated with cardioprotection (odds ratio [OR], 0.23; 95% CI, 0.08-0.65; \( P=0.005 \)), whereas trials in which the estimated maximal heart rate was >100 bpm did not demonstrate cardioprotection (OR, 1.17; 95% CI, 0.79-1.80; \( P=0.43 \)), suggesting that effective heart rate control is important in achieving cardioprotection. Importantly, in the context of the question of heart rate control in clinical practice, 25% of patients receiving \( \beta \)-blockers had episodes during which their heart rate was over 100 bpm, demonstrating that administration of \( \beta \)-blockers does not reliably decrease heart rate in all patients. Furthermore this meta-analysis highlighted the risks of increased side effects, including bradycardia, supporting the judicious use of combination therapy with other drugs to achieve effective postoperative control of heart rate.

\section*{Heart rate control in stable angina}

The area in which data on the control of heart rate in clinical practice is particularly sparse—despite its relevance—is stable angina. Specific questions include those relating to the resting heart rate patterns of patients with stable angina both on and off medication to reduce heart rate, the effects of heart rate on clinical decisions made by cardiologists who are treating patients with stable angina and the clinical scenarios that mediate against tight control of heart rate, the appropriateness of the use of available agents to reduce heart rate, and the effect of appropriate heart rate control on outcome. Studies are emerging, however, that offer to cast light on this important issue.

The Euro Heart Survey on Angina was a prospective, observational, cohort study of patients with stable angina presenting to cardiology services for the first time. Consecutive outpatients with a clinical diagnosis made by a cardiologist were enrolled, and 3779 patients were included in the analysis.\(^{28}\) Patients with stable angina caused by myocardial ischemia secondary to coronary disease were included. The survey was carried out in community-based, ambulatory individuals newly presenting to a cardiologist. The majority of patients had been referred by their primary care physician, with under 10% being self referrals, and the remainder having been referred by general physicians or accident and emergency physicians. Enrolment took place at 197 centers in 36 countries in Europe and the Mediterranean basin.

Although there was marked regional heterogeneity in prescribing patterns, overall, after initial assessment by a cardiologist, 67% of patients were taking (or were recommended to take) a \( \beta \)-blocker, 61% a nitrate, and 27% a calcium channel blocker.\(^{29}\) Most patients (59%) received two or more antianginal drugs, and only 13% received no antianginal therapy. Despite approximately a third of patients taking \( \beta \)-blockers at baseline, the overall mean resting heart rate was 73 bpm.\(^{30}\) Other important points that have been highlighted by this survey are the fact that resting heart rate is affected by comorbid conditions such as chronic respiratory disease and diabetes, with higher resting heart rates recorded in patients with these conditions. \( \beta \)-Blockers are less fre-
fluently prescribed in patients with chronic respiratory disease or diabetes, and crucially, the doses of β-blockade used by both primary physicians and cardiologists were found to be subtherapeutic. These findings clearly point to concern regarding the potential for side effects.

Current treatment options to reduce heart rate chiefly comprise β-blockers and calcium channel blockers, although selective 
I channel inhibitors such as ivabradine are a newer addition to the armamentarium. 

The evidence for the potential of ivabradine to reduce heart rate is compelling and was supported by the results of the first randomized, double-blind, placebo-controlled ivabradine trial, the MERIT-HF (Multicenter End-Point II Heart Failure) trial, which enrolled 3232 patients with chronic heart failure and left-ventricular ejection fraction of ≤35% who were already receiving standard medical therapy with diuretics, angiotensin-converting enzyme inhibitors, and β-blockers. 

The addition of ivabradine to standard therapy was associated with a significant further improvement in the primary endpoint of the study, which was a composite of all-cause mortality or hospitalization for heart failure at 24 months. The average heart rate reduction of 9 bpm was significant, allowing the patients to reach the recommended heart rate level of less than 60 bpm. This heart rate reduction was associated with a significant further improvement in all exercise testing parameters, with no unfavorable effects on safety or tolerability.

Conclusion

The evidence for targeted heart rate lowering is growing, and there is emerging evidence that a gap exists between guidelines and practice in managing heart rate in the CAD population. The challenge to the cardiology community is twofold: (i) to refine our current knowledge regarding the effect of heart rate lowering on clinical events according to the agents used, the optimal doses, and the specific different clinical presentations of CAD; and (ii) to rapidly translate this evidence into practice.

References

25. Rabk AE, Brull SJ, Timmer F, et al. The effect of heart rate control on myocardial...


**Keywords:** acute coronary syndromes; myocardial infarction; stable angina; heart rate; independent cardiovascular risk factor; β-blocker; calcium channel blocker; ivabradine

**La fréquence cardiaque est-elle contrôlée de façon optimale chez les patients coronariens en pratique clinique ?**

La demande myocardique en oxygène est principalement contrôlée par la fréquence cardiaque qui contrôle aussi l’apport myocardique en oxygène et une fréquence cardiaque élevée peut déclencher une ischémie myocardique. De nouvelles preuves suggèrent de plus que la fréquence cardiaque pourrait être aussi importante, comme facteur de risque cardiovasculaire indépendant, que le tabagisme, la dyslipidémie ou l’hypertension, ceci étant encore souvent négligé. Il existe peu de données sur le contrôle de la fréquence cardiaque en pratique clinique et celles qui existent, par exemple dans des registres de syndromes coronaires aigus et dans des populations ayant subi un infarctus du myocarde, suggèrent qu’une fréquence cardiaque élevée est fréquente. Chez une proportion importante de patients en post-infarctus du myocarde (jusqu’à un tiers des femmes et un quart des hommes), la fréquence cardiaque de repos est supérieure à 75 bpm, niveau au-dessus duquel le risque d’événements cardiaques commence à augmenter. Des données observationnelles provenant d’études sur le blocage préopératoire des récepteurs β et des métaanalyses sur l’effet de ce blocage sur la diminution de la mortalité ont montré l’extrême variabilité inter-patients dans la réponse de la fréquence cardiaque aux β-blockants. Une grande proportion de patients (plus de 25 %) n’atteint pas la fréquence cardiaque ciblée et une cardioprotection efficace par β-blockants nécessite que ce but soit atteint. D’après l’Euro Heart Survey of Angina, le contrôle de la fréquence cardiaque n’est pas optimal dans le cadre de l’angoor stable malgré ses bénéfices évidents en termes de diminution de l’ischémie, de nombreux facteurs, comme la comorbidité, influant sur l’usage des β-blockants.
Coronary artery disease remains a major global public health problem. Treatment includes drugs to control anginal symptoms and myocardial ischemia, and treatment to improve clinical outcomes. The latter includes not only recommended lifestyle changes and drugs to control risk factors, but also a series of drugs with established efficacy in preventing adverse cardiac outcomes, such as antithrombotic agents, statins, renin-angiotensin system blockers, and β-blockers. Ivabradine is a specific inhibitor of the If current, whose action produces selective heart rate reduction in patients with elevated heart rate, without adverse hemodynamic side effects. It has established efficacy in preventing or limiting anginal symptoms and myocardial ischemia, and in head-to-head comparisons, yields comparable efficacy to that of atenolol on exercise-induced ischemia. A recent trial, ASSOCIATE (evaluation of the Antianginal efficacy and Safety of the aSsociation Of the If Current Inhibitor ivAbradine with a beTa-blockEr), demonstrated that when added to chronic treatment with β-blockers, ivabradine further reduces heart rate and improves exercise capacity while being well tolerated. Ivabradine has also now been tested in a large outcome trial, BEAUTIFUL (morBidity mortality EvaLuation of the If inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction), in patients with stable coronary artery disease and left ventricular dysfunction. While it did not affect the primary composite endpoint of cardiovascular death and hospitalization for acute myocardial infarction or heart failure, it did, in a prespecified subset analysis, reduce coronary events in patients with a baseline heart rate $\geq 70$ bpm. Thus, ivabradine has the ability to affect not only anginal symptoms or myocardial ischemia, but also to improve clinical outcomes, which makes it an important agent in the management of patients with coronary artery disease with an elevated heart rate.

Coronary artery disease is a major public health problem worldwide...
is the single most frequent cause of death in these countries. Among cardiovascular diseases, coronary artery disease (CAD) is itself the most frequent cause of mortality and morbidity. Just as an example of the public health burden associated with CAD, it is estimated that in the USA alone, every 26 seconds somebody will suffer from an acute coronary event, and every minute someone will die from one. Even among patients with stable CAD receiving modern therapy for secondary prevention, the rate of major adverse cardiac events remains high: data from the recent REDuction of Atherothrombosis for Continued Health (REACH) registry have shown that the yearly rate of cardiovascular death, myocardial infarction, and stroke is approximately 4.5%, and that an additional 10% of these patients require hospitalization for cardiovascular reasons every year.

**Treatment for coronary artery disease**

- **General therapeutic measures**
  
  Modern therapy for patients with CAD aims to control anginal symptoms, thereby improving exercise capacity and quality of life. But it also aims to prevent adverse cardiovascular events and improve outcomes. Such treatment includes lifestyle modifications (encouraging patients to quit smoking, to be physically active, and to maintain a healthy diet and a normal body mass index) and drug treatments to control risk factors such as hypertension, dyslipidemia, and diabetes.

- **Treatment to improve clinical outcomes**
  
  In addition to strict control of risk factors, four categories of agents have established benefits on clinical outcomes in the context of acute coronary syndromes, while remarkably effective at improving outcomes in the context of stable coronary syndromes. It has little impact, if any, on clinical outcomes in patients with stable CAD. In the recent Clinical Outcomes Utilizing Revascularization And Aggressive drug Evaluation (COURAGE) trial found no additional benefit of an initial strategy of routine revascularization on top of optimal medical therapy compared with medical therapy alone.

**Ivabradine: an antianginal agent**

Ivabradine (Procoralan®) is an agent that inhibits the $I_{f}$ current of the sinoatrial node, thereby slowing the heart rate of patients with sinus rhythm. Because of the importance of heart rate in myocardial oxygen consumption, reductions in heart rate are associated with a potent anti-ischemic and antianginal effect.

Since ivabradine is a pure heart rate-reducing agent, it has no negative effect on inotropy, preserves left ventricular relaxation, does not lead to coronary vasoconstriction, preserves atrioventricular and intraventricular conduction, and has no effect on blood pressure. In addition, ivabradine can be added to other antianginal agents and has excellent tolerability and safety. The principal side effect is rare, minor, and reversible visual disturbances, because some retinal cells also harbor the $I_{f}$ current.
Clinical trials have established the potent antianginal effects of ivabradine. In randomized trials, compared with placebo, ivabradine demonstrated dose-dependent improvements in exercise tolerance and prevention of exercise-induced ischemia. In the INternational TriAl on the Treatment of angina with IVabradinE versus atenolol (INITIATIVE), ivabradine was compared with β-blocker therapy with atenolol, an established treatment for prevention of exercise-induced angina, using stress tests, in 939 patients. In that study, ivabradine was noninferior to 100 mg of atenolol, with a strong trend toward superiority of ivabradine. Indeed, in that trial, when 7.5 mg ivabradine twice daily was compared with 100 mg atenolol four times daily, all the parameters of the exercise treadmill test (ie, exercise duration, time to limiting angina, time to angina onset, and time to 1-mm ST-segment depression) fulfilled criteria for noninferiority with ivabradine compared with atenolol (Figure 1). In addition, when examining the increase in exercise capacity (measured by increase in total exercise duration) provided by each beat reduction in heart rate, the “efficiency” of heart rate reduction with ivabradine was greater than that achieved by atenolol (increase in total exercise duration of 10.1 vs 5.6 seconds).

A recent trial, ASSOCIATE (evaluation of the Antianginal efficacy and Safety of the AsSociation Of the I1 Current Inhibitor ivAbradine with a βTa-BlockEd), examined the effects of ivabradine in patients with chronic stable angina pectoris receiving β-blocker therapy. In this double-blind trial, 899 patients who were all on 50 mg of atenolol daily were randomly assigned to additional treatment with either ivabradine up to 7.5 mg twice daily or placebo. Patients were then studied using exercise treadmill tests at the trough of drug activity 2 and 4 months later. Compared with placebo, and in these patients who were already on atenolol, ivabradine treatment led to improved total exercise duration on all parameters of the exercise test at 2 and 4 months (Figure 2). In addition, treatment was well tolerated, with only 1% of patients stopping drug therapy because of bradycardia. Minor reversible visual effects (phosphenes and blurred vision) were reported in 2% of ivabradine-treated patients and 0.9% of the placebo-treated patients. Thus, it had already been established that ivabradine is an effective and well-tolerated antianginal agent, alone or in combination with other drugs. ASSOCIATE now also demonstrates that when added to chronic treatment with β-blockers, ivabradine further reduces heart rate and improves exercise capacity, while being well tolerated.

Figure 1. Efficacy of ivabradine versus atenolol on exercise tolerance test parameters at trough of drug activity in the INternational TriAl on the Treatment of angina with IVabradinE versus atenolol (INITIATIVE).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Atenolol 100 mg od better</th>
<th>Ivabradine 7.5 mg bid better</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total exercise duration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to limiting angina</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to angina onset</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to 1-mm ST-segment depression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Equivalence limits</td>
<td>-35 seconds</td>
<td>+35 seconds</td>
</tr>
</tbody>
</table>
| Impact of ivabradine on clinical outcomes in patients with coronary artery disease

In order to assess whether treatment with ivabradine was associated not only with symptomatic benefits, but also with improvement in clinical outcomes, several trials have been initiated in patients with CAD. The first of these trials is BEAUTIFUL (morBidity-mortality EvAluATion of the I1 inhibitor ivabradine in patients with coronary disease and left ventricULar dysfunctlion). This is a large international, double-blind, randomized clinical trial of ivabradine versus placebo on top of optimal medical therapy, in patients with stable CAD, a baseline heart rate of at least 60 beats per minute (bpm), and left ventricular dysfunction (defined as a left ventricular ejection fraction of <40%). The primary end point was a composite of cardiovascular death and hospitalization for acute myocardial infarction or heart failure. Almost 11 000 patients were enrolled.
in 33 countries. After a median follow-up of 19 months, ivabradine did not affect the primary end point in the overall trial (hazard ratio [HR], 1.00; 95% confidence interval [CI], 0.85-1.10; \( P = 0.94 \)) nor in a prespecified subgroup of patients with a heart rate of 70 bpm or greater (HR, 0.91; 95% CI, 0.81-1.04; \( P = 0.17 \)). It did, however, reduce secondary end points in that subset: admission to hospital for fatal and nonfatal myocardial infarction (HR, 0.64; 95% CI, 0.49-0.84; \( P = 0.001 \)) and coronary revascularization (HR, 0.70; 95% CI, 0.52-0.93; \( P = 0.016 \) (Table, Figure 3).

Importantly, these results were achieved despite the fact that patients were receiving excellent background medical therapy, with high rates of the use of antithrombotics, statins, and renin-angiotensin system blockers, and more importantly, with 87% of the patients on \( \beta \)-blockers. It is important to put these

<table>
<thead>
<tr>
<th>Predefined end point</th>
<th>Hazard ratio</th>
<th>Event rate</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatal MI</td>
<td>0.68</td>
<td>28</td>
<td>41</td>
</tr>
<tr>
<td>Hospitalization for MI</td>
<td>0.64</td>
<td>85</td>
<td>131</td>
</tr>
<tr>
<td>Hospitalization for MI or unstable angina</td>
<td>0.78</td>
<td>143</td>
<td>182</td>
</tr>
<tr>
<td>Hospitalization for MI, unstable angina or revascularization</td>
<td>0.77</td>
<td>176</td>
<td>226</td>
</tr>
<tr>
<td>Coronary revascularization</td>
<td>0.70</td>
<td>76</td>
<td>108</td>
</tr>
</tbody>
</table>

Table. Reduction of the risk of coronary events in patients with a heart rate \( \geq 70 \) beats per minute in BEAUTIFUL (morBidity-mortal- ity EvaAlItion of the \( \beta \)-inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction). MI, myocardial infarction.
results into perspective using the analysis done in the placebo group of the same trial, looking at the impact of heart rate at baseline on clinical outcomes. In that analysis, it was apparent that heart rate is a strong prognostic factor in patients with CAD and left ventricular dysfunction, and that in fact, an elevated heart rate (≥70 bpm) identifies those at increased risk of cardiovascular outcomes, with a differential effect on outcomes associated with heart failure and outcomes associated with coronary events: the risk of mortality and heart failure increased continuously with increasing heart rate, whereas the impact of heart rate on coronary events appeared to increase above the threshold of 70 bpm. This suggests that the value of 70 bpm is probably a key threshold in CAD, which deserves consideration in making decisions regarding treatment of these patients (Figures 4-6).

These findings have two important implications: first, from a pathophysiologic standpoint, the fact that a drug that specifically slows the heart rate without affecting any of the other determinants of oxygen consumption or any other hemodynamic parameter would affect clinical outcomes, demonstrates that the relationship between elevated heart rate and adverse cardiovascular outcomes that has been demonstrated in several important observational studies is not solely an association, but is at least in part, causal, since ivabradine has no other hemodynamic action other than slowing sinus rhythm. In addition, from a clinical standpoint, they provide evidence of a benefit of ivabradine far beyond the mere control of anginal symptoms. It now belongs to the small number of drugs that have established prognostic benefits on hard clinical outcomes in patients with CAD, even when such patients receive excellent background medical therapy. This indicates that ivabradine should now be considered for the management of patients with CAD, left ventricular dysfunction, and a heart rate of ≥70 bpm. It is plausible that these benefits may extend to a similar patient population but who are without left ventricular dysfunction, but this deserves to be tested in a second trial, which is indeed ongoing.

Conclusion

Given the burden that CAD imposes on global public health, it is important to find new treatments that are able to improve clinical outcomes in patients with CAD. Ivabradine is a new treatment that selectively slows the heart rate and is associated with established efficacy against angina and exercise-induced myocardial ischemia. It has comparable efficacy to that of atenolol, an established treatment for angina, but also provides additional efficacy when added to β-blockers (as recently demonstrated in ASSOCIATE) or to other antianginal background therapy.

BEAUTIFUL showed that in addition to symptomatic improvement, treatment with ivabradine also yields improved clinical outcomes in terms of prevention of fatal or nonfatal myocardial infarction or the need for myocardial revascularization in patients with a baseline heart rate ≥70 bpm when added to modern background therapy. Both prevention of myocardial infarction and reduction of the need for myocardial revascularization are likely to have a substantial impact on global health and health costs. Ivabradine (Procacin®) therefore has an important role in the management of patients with stable CAD.

References

NEW INSIGHTS INTO \( I_f \) INHIBITION: FROM ISCHEMIA PREVENTION TO IMPROVEMENT IN CORONARY OUTCOMES


Keywords: coronary artery disease; angina; myocardial ischemia; risk factor; clinical outcome; heart rate elevation; treatment; ivabradine

LA PLACE DE L’IVABRADINE DANS LA PRISE EN CHARGE DES PATIENTS CORONAIENRS : NOUVEL APERÇU

La maladie coronaire demeure un problème de santé publique majeur global. Sa prise en charge comprend des médicaments qui contrôlent les symptômes angoreux et l’ischémie myocardique et des traitements qui améliorent l’évolution clinique. Ces derniers comportent, outre les modifications recommandées de style de vie et des médicaments qui agissent sur les facteurs de risque, des médicaments comme les antithrombotiques, les statines, les inhibiteurs du système rénine-angiotensine et les bêtabloquants dont l’efficacité dans la prévention des événements cardiaques indésirables est prouvée. L’ivabradine est un inhibiteur spécifique du courant \( I_f \) qui ralentit sélectivement la fréquence cardiaque chez les patients ayant une fréquence cardiaque élevée, sans effet hémodynamique indésirable. Son efficacité est prouvée dans la prévention ou la limitation des symptômes angoreux et de l’ischémie myocardique et, équivalente à celle de l’aténolol sur l’ischémie d’effort lorsqu’on les compare point par point. La récente étude ASSOCIATE (evaluation of the Antianginal efficacy and Safety of the aSsociation Of the \( I_f \) Current Inhibitor ivAbradine with a beTa-blockEr), a montré que l’ivabradine, associée aux bêtabloquants au long cours, ralentit davantage la fréquence cardiaque et améliore la capacité à l’effort avec une bonne tolérance. La grande étude de résultats BEAUTIFUL (morBidity mortality EvAUnaTion of the \( I_f \) inhibitor ivabradine in patients with coronary disease and left ventricULar dysfunction) a également évalué l’ivabradine chez les patients atteints de maladie coronaire stable et de dysfonction ventriculaire gauche. Dans une sous-analyse présélectionnée, l’ivabradine diminue les événements coronaires chez les patients dont la fréquence cardiaque est supérieure à 70 bpm, même chez ceux dont le traitement de fond est excellent, sans influer sur le critère primaire composite de décès cardiovasculaire et d’hospitalisation pour infarctus aigu ou insuffisance cardiaque. L’ivabradine peut donc agir non seulement sur les symptômes angoreux ou l’ischémie myocardique, mais aussi améliorer les résultats cliniques, ce qui en fait un médicament important dans la prise en charge des patients coronariens ayant une fréquence cardiaque élevée.
Lessons from BEAUTIFUL: new frontiers in heart rate control

by Å. Hjalmarson, Sweden

Elevated heart rate is an independent risk predictor among patients with coronary artery disease (CAD). Studies on the use of β-blockers in patients after myocardial infarction (MI) or with chronic heart failure have previously reported improved outcome and reduced mortality and morbidity, especially among patients with elevated heart rate at baseline. BEAUTIFUL (morbidity-mortality Evaluation of the If inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction) was designed to test whether ivabradine, a specific inhibitor of the If current in the sinoatrial node with pure heart rate-lowering ability, could reduce mortality and morbidity in patients with CAD and left ventricular ejection fraction <40%. 10,917 patients were randomized in a double-blind, parallel-group trial to receive ivabradine (n=5479) titrated to an average dose of 6.2 mg twice daily, or placebo (n=5438). Patients were receiving optimal cardioprotective medication including β-blockers (87%) and angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers (90%). At 6 months, compared with placebo, ivabradine reduced heart rate by 7.2 beats per minute (bpm), and by 9 bpm in the subgroup with baseline heart rate of ≥70 bpm. There was no significant effect on the primary composite end point—cardiovascular death, admission to hospital for acute MI or for new onset or worsening heart failure—nor on mortality, heart failure, and coronary end points. In a prespecified subgroup with a baseline heart rate of ≥70 bpm (n=5492), there was a significant effect on coronary end points including admission to hospital for MI or unstable angina or the need for revascularization. Treatment was well tolerated. Ivabradine can be safely used in conjunction with β-blockers and may also improve coronary outcome in patients with baseline heart rates of ≥70 bpm.

Medicographia. 2009;31:377-383 (see French abstract on page 383)

Heart rate is an independent risk predictor for the onset of acute coronary events, including all-cause mortality, cardiovascular mortality, sudden cardiac death, and acute coronary syndromes. This has been demonstrated in healthy subjects, patients with risk factors such as hypertension, hyperlipidemia, and diabetes, as well as in patients with established coronary artery disease with angina pectoris, myocardial infarction, arrhythmias, and chronic heart failure. Elevated heart rate has also been found to play a role in the development and progression of atherosclerosis and coronary artery disease resulting in myocardial infarction, sudden death, and chronic heart failure.
Heart rate reduction

β-Blockers were the first class of drugs for which there was a clear demonstration of their ability to reduce mortality and the number of hospitalizations in patients with acute myocardial infarction; this was shown in patients treated with timolol, metoprolol, and propranolol.12 Upon pooling data from major placebo-controlled β-blocker trials in patients with acute myocardial infarction, Kjekshus proposed that there was a significant relationship between reduction in resting heart rate and a decrease in all-cause mortality. The β-blockers that reduced heart rate by about 12-15 beats per minute (bpm) reduced mortality by more than 30%, while those that produced a smaller or no reduction in heart rate had no significant effect on mortality. A review of studies on chronic heart failure showed a similar relationship between changes in heart rate and all-cause mortality with the use of β-blockers (Figure 1).13 In the two large trials in patients with chronic heart failure, ME TOPROLOL CR/XL Randomized Intervention Trial in congestive Heart Failure (MERIT-HF) and Cardiac Insufficiency Bisoprolol Study–II (CIBIS-II), patients with the highest heart rates at baseline had the highest mortality, and among these patients, there was a more marked effect with the β-blockers bisoprolol and metoprolol CR/XL. A meta-regression analysis of randomized controlled clinical trials confirmed that the beneficial effect of β-blockers and calcium channel blockers on mortality in post–myocardial infarction patients was related to reduction in resting heart rate.14 Because of the beneficial effects of β-blockers, it has been generally accepted and also stated in international guidelines that β-blockers should be used in patients suffering from acute myocardial infarction or chronic heart failure in order to reduce mortality and morbidity.15 Since more marked effects have been seen in subgroups of patients with elevated heart rate, it has been assumed that heart rate reduction per se is of major importance in the effect of β-blockers on outcome. However, β-blockers do not only reduce heart rate, but have, in addition, a number of potential beneficial effects resulting from their blocking action, for example, their effects on sympathetic activation. It is well known that sympathetic activation and catecholamines increase the risk of serious ventricular arrhythmias and ventricular fibrillation in animal experimental models of acute myocardial ischemia.16 In large placebo-controlled clinical trials, both in patients with myocardial infarction and in patients with chronic heart failure, β-blockers have been found to have a very marked effect on the incidence of sudden cardiac death.18 In fact, the effects on sudden cardiac death are in general more marked than the overall effects on total mortality or on other modes of death.17 This may be due to a specific antiarrhythmic effect of β-blockers.18

Ivabradine is a novel specific heart rate–lowering agent that acts in sinoatrial node cells by selectively and specifically inhibiting the I f pacemaker current in a dose-dependent manner.19 As a result, it is a pure heart rate–lowering agent in patients with sinus rhythm. Ivabradine does not affect blood pressure, myocardial contractility, intraventricular conduction, or ventricular repolarization.19,20 It has antianginal effects comparable to those of β-blockers, and is used in patients with angina pectoris with an approved clinical indication.21 Treatment with ivabradine therefore provides an opportunity to assess the effects of lowering heart rate, without directly altering other aspects of cardiac function.

**BEAUTIFUL design and results**

BEAUTIFUL (morBidity-mortality EvAIUaTion of the I f inhibitor ivabradine in patients with coronary disease and left ventricUlar dysfunction) was designed to test whether the addition of ivabradine to standard treatment to lower heart rate can reduce cardiovascular deaths and morbidity in patients with stable coronary artery disease and left ventricular systolic dysfunction.22 This randomized double-blind placebo-controlled trial was performed at 781 centers in 33 countries. A total of 10,917 patients with coronary artery disease and a left ventricular ejection fraction of ≤40% were randomized: 5,479 of these patients received 5 mg of ivabradine with the intention of increasing the dose to the target of 7.5 mg twice a day, and 5,438 received matching placebo in addition to op-
timal cardiovascular medication. The primary end point was a composite of cardiovascular death, admission to hospital for acute myocardial infarction, and admission to hospital for new onset or worsening of heart failure. Patients eligible for inclusion were males and females aged 55 years or older (or 18 years or older if diabetic) with coronary artery disease, a left ventricular ejection fraction of <40%, and an end-diastolic internal dimension of greater than 56 mm on echocardiography. Patients had to be in sinus rhythm with a resting heart rate of ≥60 bpm.

During the course of the study, publication of other studies indicated that heart rate was only important as a predictor of outcome when it was elevated above 70-75 bpm. It was therefore prespecified in the protocol that one should analyze the effect of ivabradine in a subgroup of patients with a heart rate of ≥70 bpm. The Table shows the baseline characteristics of the ivabradine and placebo groups. It can be seen that 88% of the patients had a history of myocardial infarction, 52% had previous revascularization, 37% a history of diabetes, and left ventricular ejection fraction was on average about 32% in both groups. It can also be seen that 84% of the patients were in New York Heart Association (NYHA) class II-III, indicating that this is a study not only in patients with systolic dysfunction, but also in a majority with symptomatic heart failure. Furthermore, it can be seen that 87% of the patients were on β-blocker treatment, and 90% were on an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker. The subgroup of patients with a prespecified heart rate of ≥70 bpm included 5392 patients, and among these patients, the baseline characteristics did not differ between the ivabradine and the placebo groups.

One month after randomization, the mean dose of ivabradine was 6.2 mg twice daily, and at 6 months after randomization, the difference in heart rate between the two groups was seen that 88% of the patients had a history of myocardial infarction, 52% had previous revascularization, 37% a history of diabetes, and left ventricular ejection fraction was on average about 32% in both groups. It can also be seen that 84% of the patients were in New York Heart Association (NYHA) class II-III, indicating that this is a study not only in patients with systolic dysfunction, but also in a majority with symptomatic heart failure. Furthermore, it can be seen that 87% of the patients were on β-blocker treatment, and 90% were on an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker. The subgroup of patients with a prespecified heart rate of ≥70 bpm included 5392 patients, and among these patients, the baseline characteristics did not differ between the ivabradine and the placebo groups.

During the course of the study, publication of other studies indicated that heart rate was only important as a predictor of outcome when it was elevated above 70-75 bpm. It was therefore prespecified in the protocol that one should analyze the effect of ivabradine in a subgroup of patients with a heart rate of ≥70 bpm. The Table shows the baseline characteristics of the ivabradine and placebo groups. It can be seen that 88% of the patients had a history of myocardial infarction, 52% had previous revascularization, 37% a history of diabetes, and left ventricular ejection fraction was on average about 32% in both groups. It can also be seen that 84% of the patients were in New York Heart Association (NYHA) class II-III, indicating that this is a study not only in patients with systolic dysfunction, but also in a majority with symptomatic heart failure. Furthermore, it can be seen that 87% of the patients were on β-blocker treatment, and 90% were on an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker. The subgroup of patients with a prespecified heart rate of ≥70 bpm included 5392 patients, and among these patients, the baseline characteristics did not differ between the ivabradine and the placebo groups.

During the course of the study, publication of other studies indicated that heart rate was only important as a predictor of outcome when it was elevated above 70-75 bpm. It was therefore prespecified in the protocol that one should analyze the effect of ivabradine in a subgroup of patients with a heart rate of ≥70 bpm. The Table shows the baseline characteristics of the ivabradine and placebo groups. It can be seen that 88% of the patients had a history of myocardial infarction, 52% had previous revascularization, 37% a history of diabetes, and left ventricular ejection fraction was on average about 32% in both groups. It can also be seen that 84% of the patients were in New York Heart Association (NYHA) class II-III, indicating that this is a study not only in patients with systolic dysfunction, but also in a majority with symptomatic heart failure. Furthermore, it can be seen that 87% of the patients were on β-blocker treatment, and 90% were on an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker. The subgroup of patients with a prespecified heart rate of ≥70 bpm included 5392 patients, and among these patients, the baseline characteristics did not differ between the ivabradine and the placebo groups.

One month after randomization, the mean dose of ivabradine was 6.2 mg twice daily, and at 6 months after randomization, the difference in heart rate between the two groups was seen that 88% of the patients had a history of myocardial infarction, 52% had previous revascularization, 37% a history of diabetes, and left ventricular ejection fraction was on average about 32% in both groups. It can also be seen that 84% of the patients were in New York Heart Association (NYHA) class II-III, indicating that this is a study not only in patients with systolic dysfunction, but also in a majority with symptomatic heart failure. Furthermore, it can be seen that 87% of the patients were on β-blocker treatment, and 90% were on an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker. The subgroup of patients with a prespecified heart rate of ≥70 bpm included 5392 patients, and among these patients, the baseline characteristics did not differ between the ivabradine and the placebo groups.

### Table

<table>
<thead>
<tr>
<th>Baseline characteristics of the BEAUTIFUL (morBidity–mortality EvalUatIon of the I f inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction) study population.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ivabradine group</strong></td>
</tr>
<tr>
<td><strong>Demographic characteristics</strong></td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Sex (male)</td>
</tr>
<tr>
<td>Smoking (current)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
</tr>
<tr>
<td><strong>Medical history</strong></td>
</tr>
<tr>
<td>History of hypertension</td>
</tr>
<tr>
<td>History of diabetes</td>
</tr>
<tr>
<td>History of dyslipidemia</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
</tr>
<tr>
<td>Previous percutaneous coronary intervention</td>
</tr>
<tr>
<td>NYHA class I heart failure</td>
</tr>
<tr>
<td>NYHA class II heart failure</td>
</tr>
<tr>
<td>NYHA class III heart failure</td>
</tr>
<tr>
<td><strong>Medication at randomization</strong></td>
</tr>
<tr>
<td>Aspirin or antithrombotic agent</td>
</tr>
<tr>
<td>Statin</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker, or both</td>
</tr>
<tr>
<td>β-Blocker</td>
</tr>
<tr>
<td>Organic nitrates</td>
</tr>
<tr>
<td>Diuretics (excluding antialdosterone)</td>
</tr>
<tr>
<td>Antialdosterone agents</td>
</tr>
</tbody>
</table>
7.2 bpm. In the subgroup of patients in whom heart rate was ≥70 bpm at baseline, the difference in heart rate between the two groups was 9 bpm at 6 months.

Figure 2 shows that there was no treatment effect on the composite primary end point in the total study population. There was a nonsignificant favorable trend with ivabradine regarding hospital admission for myocardial infarction and coronary revascularization. The treatment was well tolerated with a similar number of serious adverse events in the two groups. Interestingly, visual symptoms were unexpectedly rare (0.5%). In the ivabradine group, 28% discontinued the study medication, compared with 16% in the placebo group. This difference in discontinuation was mainly explained by the fact that 13% of the patients in the ivabradine group had bradycardia, compared with 2% in the placebo group.

In the prespecified subgroup with a heart rate of ≥70 bpm, ivabradine tended to reduce the primary composite end point (9%; nonsignificant). However, as can be seen from Figure 3, in the group of patients with a heart rate of ≥70 bpm, ivabradine significantly reduced admission to hospital for myocardial infarction (P<0.001) and admission to hospital for myocardial infarction or unstable angina (P=0.02). As can be seen in Figure 4, there was also a reduction in the proportion of patients who underwent coronary revascularization (P=0.016).

Subanalysis was carried out on the placebo group to test the hypothesis that elevated resting heart rate at baseline is a marker for subsequent cardiovascular death and morbidity.23 In Figure 5 it can be seen that a heart rate of ≥70 bpm was a highly significant and independent predictor of cardiovascular death, admission to hospital for heart failure, admission to hospital for myocardial infarction, and the use of coronary revascularization.
Discussion of BEAUTIFUL results

It was clearly demonstrated in BEAUTIFUL, this large trial in patients with coronary artery disease and left ventricular dysfunction, that ivabradine at an average dose of 6.2 mg twice daily had no effect at all on mortality or morbidity in patients with a heart rate of between 60 and 70 bpm. However, in patients with a basal heart rate of >70 bpm, there was a marked reduction in admission to hospital for myocardial infarction (36%; P<0.001), and additionally significant effects on admission to hospital for myocardial infarction or unstable angina, or coronary revascularization (22%-30% reduction). One major question is whether the heart rate reduction with ivabradine was too small to be effective on outcomes. In BEAUTIFUL, ivabradine reduced heart rate by 6 bpm at 12 months and 5 bpm at 24 months. The major β-blocker trials in myocardial infarction with timolol, metoprolol, and propranolol reduced heart rate by 12-15 bpm.22 In two of the major β-blocker trials in heart failure (MERIT-HF and OIS-BIS-III),23,24 heart rate was reduced by about 11 bpm. It should be noted that 87% of the patients in BEAUTIFUL were on a β-blocker (84% among patients with baseline heart rate of >70 bpm).

Even if the β-blocker dose had been doubled, it is most likely that further heart rate reduction would not have exceeded 5%-6% (ie, comparable to the effect of ivabradine).

Are the patients in BEAUTIFUL comparable to those of the β-blocker trials? In fact, most similar is the CArvedilol Postinfarct suRvIval COntrol in left veNtricular dysfunction (CAPRICORN) trial comparing carvedilol with placebo in patients after myocardial infarction with left ventricular dysfunction.24 In this trial, baseline ejection fraction was 33% (mean patient age 63 years, follow-up 16 months), and all-cause mortality with carvedilol was 12% at 16 months. Corresponding figures for BEAUTIFUL were ejection fraction 32%, age 65 years, and 10% mortality (87% were on β-blockers). In CAPRICORN, all-cause mortality was reduced by 23%. This is similar to that reported in a meta-analysis of 22 long-term randomized controlled trials of the effects of β-blockers after acute myocardial infarction.23 It is important to note, however, that in CAPRICORN as well as in other post-infarct survival studies with β-blockers, the β-blocker was given within 3 to 21 days after myocardial infarction. This particular group...
of post-myocardial infarction patients was specifically excluded from BEAUTIFUL, which focused on patients with stable coronary artery disease.

In the β-blocker arms of the two major heart failure trials on β-blockers (MERIT-HF and CIBIS-II), there was a 19-month mortality rate of around 10%, as in BEAUTIFUL, although both β-blocker trials included patients with NYHA Class IV heart failure, who were excluded from BEAUTIFUL. However, in these trials, the β-blockers metoprolol XR/CL and bisoprolol reduced all-cause mortality by 35% and sudden cardiac death by more than 40%. Also in these trials, the β-blockers reduced heart rate by about 11%. A question is whether further heart rate reduction of 5%-6% (as with ivabradine in BEAUTIFUL) from an increase in the dose of the β-blockers would have caused any further reduction in mortality and morbidity.

During the progress of BEAUTIFUL, the steering committee realized that a higher baseline heart rate meant higher mortality and morbidity in the study patients. Furthermore, the heart rate reduction with ivabradine was more marked. This is clearly seen in Figure 6. The heart rate reduction in the higher heart rate group is similar to that seen in the β-blocker heart failure trials. It should be noted that the average baseline heart rate in MERIT-HF and CIBIS-II was 81-82 bpm and in CAPRICORN it was 77 bpm. The baseline heart rate in BEAUTIFUL was 72 bpm. There is no doubt that the effect of β-blockers on heart rate reduction and on outcome is more marked in patients with a heart rate at baseline of 70-75 bpm or higher. In fact, in the Göteborg metoprolol trial (see reference 12), there was no difference between placebo and metoprolol treatment among patients with a baseline heart rate of <70 bpm at 3 months or 2 years of follow-up. The 5000 patients with a baseline heart rate of <70 bpm in BEAUTIFUL gave a lower statistical power to the study, since these patients are less good responders to heart rate reduction. Another problem is that it is most likely that the best responders to ivabradine among patients with a baseline heart rate of <70 bpm (most of the 705 patients in the ivabradine group) were discontinued due to bradycardia. Both the inclusion and exclusion levels were 60 bpm; the exclusion level should have been lower (ie, 45-50 bpm). The most likely reason for the lack of significant effects with ivabradine on mortality and heart failure end points in BEAUTIFUL is that the optimal use of β-blockers had lowered heart rate and mortality/heart failure events. The data on the 13% of patients in the trial who were not on a β-blocker is of limited value by way of a lack of statistical power due to the low numbers of patients and events.

Conclusion

Ivabradine at an average dose of 6.2 mg twice daily did not improve cardiac outcomes in all patients with stable coronary heart disease and left ventricular systolic dysfunction. However, in the subgroup of patients whose heart rate was >70 bpm, there was a favorable trend toward the primary end point with ivabradine (9% reduction), but with no effect on cardiovascular death or admission to hospital for heart failure. There was a marked reduction in the coronary end points, including admission to hospital for myocardial infarction (36%; P<0.001), admission to hospital for myocardial infarction or unstable angina (22%; P=0.02), and coronary revascularization (30%; P=0.016).

The statement made by the authors of the BEAUTIFUL publication that ivabradine can be given safely to patients with coronary artery disease and impaired left ventricular dysfunction and in conjunction with β-blockers is certainly justified. In addition, the combination of ivabradine with β-blockade is not only safe, but it also seems to improve a number of coronary end points.

Figure 6. Mean heart rate during the study (A) in the total study population and (B) in the subgroup with heart rate of 70 beats per minute (bpm) or greater.

New insights into \( I_f \) inhibition: from ischemia prevention to improvement in coronary outcomes

References


Keywords: coronary artery disease; left ventricular dysfunction; cardiovascular outcome; risk predictor; heart rate reduction; \( \beta \)-blocker; ivabradine; BEAUTIFUL

Les leçons de l'étude BEAUTIFUL: un nouvel horizon pour le contrôle de la fréquence cardiaque

Une fréquence cardiaque élevée est un facteur prédictif indépendant chez les patients atteints de maladie coronaire (MC). Des études sur l'utilisation des \( \beta \)-bloquants chez des patients ayant eu un infarctus du myocarde (IDM) ou ayant une insuffisance cardiaque chronique ont rapporté antérieurement une amélioration des résultats et une réduction de la mortalité et de la morbidité, en particulier chez les patients ayant une fréquence cardiaque initiale élévéée. L'étude BEAUTIFUL (morBidity-mortality EvAlUaTion of the \( I_f \) inhibitor) ivabradine en patients avec coronary disease and left ventricular dysfunction a été conçue pour tester si l’ivabradine, un inhibiteur spécifique du courant \( I_f \), chez des patients ayant eu un infarctus du myocarde (IDM) ou ayant une MC et une fraction d’éjection ventriculaire <40 %. Une étude en double aveugle en groupes parallèles a permis de randomiser 10 917 patients pour recevoir soit de l’ivabradine (n = 5 479) administrée à une dose moyenne de 6,2 mg deux fois par jour soit un placebo (n = 5 438). Les patients recevaient un traitement cardioprotecteur optimal comprenant des \( \beta \)-bloquants (87 %) et des inhibiteurs de l’enzyme de conversion ou des antagonistes des récepteurs de l’angiotensine 2 (90 %). L’ivabradine a réduit la fréquence cardiaque de 7,2 battements par minute (bpm) à 6 mois et de 9 bpm dans le sous-groupe ayant une fréquence cardiaque initiale ≈ 70 bpm, sans aucun effet significatif sur le critère primaire composite – décès cardio-vasculaire, hospitalisation pour IDM aigu ou installation d’une insuffisance cardiaque – ni sur la mortalité, l’insuffisance cardiaque et les événements coronariens. Un effet significatif sur les événements coronariens comprenant hospitalisation pour IDM ou arrêt instable ou revascularisation a été constaté dans un sous-groupe prédisposé ayant une fréquence cardiaque initiale ≈ 70 bpm (n = 5 492). Le traitement par ivabradine a été bien toléré et peut être utilisé en toute sécurité avec les \( \beta \)-bloquants, amidonnant aussi les événements coronariens chez les patients dont la fréquence cardiaque initiale est ≈ 70 bpm.
Optimizing secondary prevention treatment in stable coronary artery disease

by L. R. Padial, Spain

Stable coronary artery disease (CAD) is an important worldwide health problem. Patients with stable CAD are at significant risk of developing subsequent cardiovascular complications that bear a high mortality; effective preventive measures against such complications are therefore necessary. Control of cardiovascular risk factors constitutes the main tool for improving prognosis in these patients. Key factors in this respect are cholesterol reduction in virtually all patients, and blood pressure reduction when needed. Furthermore, smoking should be avoided in all patients, and diabetic patients should have tight glucose control maintained. It has also been demonstrated that certain drugs (ie, antiplatelet drugs, β-blockers, angiotensin-converting enzyme inhibitors) can further improve the prognosis in some or all patients with stable CAD. Despite all of this, as demonstrated in BEAUTIFUL (morBidity-mortality EvAlUaTion of the Ii inhibitor ivabradine in patients with coronary disease and left ventricULar dysfunction), many patients with stable CAD remain at high risk due to an elevated heart rate, one of the main determinants of myocardial oxygen demand. In such patients with CAD and left ventricular dysfunction, the use of ivabradine on top of state-of-the-art preventive treatment was able to significantly reduce ischemic complications such as myocardial infarction and revascularization, although without affecting heart failure complications. Since many patients with stable CAD remain at risk despite their current treatment because of a high heart rate (over 70 beats per minute), ivabradine can help to further improve their cardiovascular prognosis.

Coronary artery disease (CAD), usually secondary to atherosclerosis, is a leading cause of death and disability in Western societies. Moreover, due to its sharply increasing prevalence in non-Western countries, it will inevitably be a major health problem worldwide in the years to come. Patients with stable CAD have a high risk of developing subsequent cardiovascular events, such as angina pectoris, myocardial infarction, and stroke. The identification and control of major cardiovascular risk factors (ie, hypertension, dyslipidemia, smoking, obesity, inactivity, and diabetes) are two of the main tasks of caregivers for patients with known CAD, as this can potentially reduce subsequent morbidity and mortality in such patients. These tasks are usually included under the term “secondary prevention.” Since not all patients comprising the “secondary prevention” category share the same risk, a group of “very high risk” subjects has been defined among

Address for correspondence: Professor Luis Rodriguez Padial, Cardiac Unit, Hospital Virgen de la Salud, Toledo, Spain (e-mail: lrodriguez@sescam.org)

www.medicographia.com
those with established CAD, in which even more aggressive control of risk factors, especially lipid levels, has to be pursued. This “very high risk” group includes patients with CAD and multiple risk factors (especially diabetes), severe or poorly controlled risk factors (especially active smoking status), multiple risk factors of the metabolic syndrome (particularly high-density lipoprotein [HDL] cholesterol <40 mg/dL and non-HDL cholesterol ≥130 mg/dL), and those with acute coronary syndromes.3

Furthermore, although secondary prevention usually applies to patients with established CAD, there are some individuals without known CAD whose risk of subsequent cardiovascular events is similar to that observed in patients with CAD.4 Such patients, regarded as having “CAD equivalent,” should be managed as aggressively as patients with established CAD. Those with noncoronary atherosclerotic disease, diabetes, chronic kidney disease (serum creatinine >1.5 mg/dL or estimated creatinine clearance rate <60 mL/min per 1.73 m²), and multiple risk factors that confer a 10-year risk larger than 20%, which comprise most metabolic syndrome patients, are among the groups included in the “CAD equivalent” category.

Comprehensive application of all available secondary prevention measures has a very important impact on CAD populations of all ages. In the USA, between 1980 and 2000, the age-adjusted CAD death rate per 100 000 population in men and women between the ages of 25 and 80 years fell from 543 to 267 in men and from 283 to 134 in women. Although several factors played a role in this mortality decrease, it is estimated that half of the reduction was due to the implementation of preventive measures.5 Furthermore, in an older population (average age of 80 years) that survived for at least 30 days after a myocardial infarction, a 3% mortality reduction was observed each year from 1995 to 2004, mostly due to the implementation of secondary preventive measures (statins, antiplatelets, etc).6 The same has been observed in CAD patients after revascularization.7,8 Despite this positive trend observed in the last decades, mortality remains high in this population, and so new treatments are needed to further improve prognosis in this high risk population.

Risk factor modification for secondary prevention of CAD will be reviewed herein (Table, page 386), with a special focus on new information regarding control of heart rate in stable CAD patients.

Control of hypertension

Several trials have demonstrated a decrease in morbidity and mortality with reduction of high blood pressure. In a metaanalysis of patients with mild to moderate hypertension, lowering of blood pressure with antihypertensive therapy decreased the rate of stroke by 40% and the rate of CAD by 16%.9 There is suggestive evidence that a blood pressure goal of less than 130/80 mm Hg, rather than the goal in the general population of less than 140/90 mm Hg, can improve outcome in patients with CAD, as in patients with diabetes and proteinuric chronic kidney disease.10

Lifestyle modifications such as moderate reduction in salt intake, weight reduction in obese patients, avoidance of excess alcohol intake—ie, limiting intake to 1 or 2 drinks a day—and regular aerobic exercise are generally recommended. When it comes to the use of antihypertensive drugs, patients with CAD appear to achieve most benefit from blood pressure reduction, but they can obtain further benefit from β-blockers, angiotensin-converting enzyme (ACE) inhibitors, or angiotensin receptor blockers (ARBs).11 Since most patients need treatment with two or more drugs to achieve the required reduction in blood pressure, small doses of diuretics and/or calcium channel blockers are frequently needed on top of the initial antihypertensive treatment.12

Lipid modification

During the last few decades, many randomized trials have shown a reduction in morbidity and mortality with cholesterol reduction, mostly with statins. More recently, several trials

SELECTED ABBREVIATIONS AND ACRONYMS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACC</td>
<td>American College of Cardiology</td>
</tr>
<tr>
<td>ACCORD</td>
<td>Action to Control Cardiovascular Risk in Diabetes (trial)</td>
</tr>
<tr>
<td>ACE</td>
<td>Angiotensin-converting enzyme</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation</td>
</tr>
<tr>
<td>AHA</td>
<td>American Heart Association</td>
</tr>
<tr>
<td>ARB</td>
<td>Angiotensin receptor blocker</td>
</tr>
<tr>
<td>BEAUTIFUL</td>
<td>morBidity-mortality Evaluation of the I f inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction</td>
</tr>
<tr>
<td>CAD</td>
<td>Coronary artery disease</td>
</tr>
<tr>
<td>DHA</td>
<td>Docosahexaenoic acid</td>
</tr>
<tr>
<td>DREAM</td>
<td>Diabetes REduction Assessment with ramipril and rosiglitazone Medication (trial)</td>
</tr>
<tr>
<td>EPA</td>
<td>Eicosapentaenoic acid</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>HbA1C</td>
<td>Glycated hemoglobin</td>
</tr>
<tr>
<td>HDL</td>
<td>High-density lipoprotein</td>
</tr>
<tr>
<td>HOPE</td>
<td>Heart Outcomes Prevention Evaluation</td>
</tr>
<tr>
<td>LDL</td>
<td>Low-density lipoprotein</td>
</tr>
<tr>
<td>LIFE</td>
<td>Losartan Intervention For Endpoint reduction in hypertension (trial)</td>
</tr>
<tr>
<td>ONTARGET</td>
<td>ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial</td>
</tr>
<tr>
<td>TRANSCEND</td>
<td>Telmisartan Randomized Assessment Study in ACE iNtolerant subjects with cardiovascular Disease</td>
</tr>
<tr>
<td>VADT</td>
<td>Veterans Affairs Diabetes Trial</td>
</tr>
</tbody>
</table>
have demonstrated a benefit with reduction of low-density lipoprotein (LDL) cholesterol to low levels such as 60-70 mg/dL in high-risk patients.13,14 The goals for LDL cholesterol levels are thus less than 100 mg/dL in CAD patients and less than 70 mg/dL in “very high risk” CAD patients as previously described.3 Both dietary modification and drug therapy should be used to obtain these targets, taking into account that drug therapy should not be delayed when the target is unlikely to be obtained early with lifestyle modification only.15 Given the enormous evidence of morbidity and mortality reduction with statins, these drugs are first-line therapy for all patients with lipid disorders. Other drugs, such as ezetimibe, can be used on top of statins if the target lipid level is not achieved.3 Statins appear to produce benefits beyond their LDL cholesterol–lowering effect; these appear to be acute and to contribute to the clinical benefits observed with these drugs.

Recent evidence has indicated the value of using high sensitivity C reactive protein to detect patients who could benefit from the use of statins to reduce their LDL cholesterol levels, in particular, in patients without known CAD, so-called primary prevention.16 This useful information may not only further expand the role of statins in cardiovascular prevention, but it could also potentially widen the number of patients without CAD that should be treated more aggressively. Obviously, more studies are warranted in this area. In patients with high levels of triglycerides (more than 200 mg/dL), the target level for non-HDL cholesterol (total cholesterol minus HDL cholesterol) should be less than 130 mg/dL.17 Fibrates are especially useful for lowering triglycerides and increasing HDL cholesterol, and are frequently used in association with statins to further reduce LDL cholesterol levels. Niacin can also be helpful in this context.

**Blood glucose control in diabetics**

Tight blood glucose control is recommended in all diabetic patients given its benefits in the reduction of microvascular and macrovascular cardiovascular complications, not only in the short term but also in the long term.18 The target level for glycated hemoglobin (HbA1C) recommended in the American College of Cardiology/American Heart Association (ACC/AHA) guidelines for patients with diabetes and CAD is less than 7%, which is the same target level advised for diabetics without CAD.1 A goal of 6.5% or less is recommended in the European Society of Cardiology guidelines.19 Certain recent findings from clinical trials have been somewhat contradictory with regard to these recommendations. The lack of a significant reduction in cardiovascular disease events with intensive blood glucose control in the clinical trials Action to Control CardiOvascular Risk in Diabetes (ACCORD),20 Action in Diabetes and VAscular disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE),21 and the VETER-
Lifestyle changes
There are some lifestyle changes that have proven benefits in cardiovascular prevention, and these are outlined below.

◆ Smoking cessation
Quitting smoking produces a reduction in cardiovascular morbidity and mortality within a matter of months, and allows achievement of a comparable risk status to nonsmokers in 3 to 5 years. Complete smoking cessation as well as avoidance of environmental tobacco smoke should be recommended in all patients with cardiovascular disease or CAD equivalent.24 Caregivers should ask patients about this habit, and advice should be given on the best strategy to stop smoking if necessary.

◆ Diet
The low level of cardiovascular mortality in Mediterranean countries has prompted recommendation regarding the Mediterranean diet, low in calories and meat, and rich in vegetables, fruits, olive oil, legumes, and nuts. Several trials have shown its benefits in patients with myocardial infarction.25 Furthermore, diets rich in omega 3 acids, found in fish, should be recommended in CAD patients, as this has been associated with a reduction in subsequent cardiovascular events in patients with myocardial infarction. Observational studies in healthy adults and randomized trials in patients with established CAD indicate that modest fish oil consumption reduces the risk of CAD death and sudden cardiac death. This is of particular importance in patients with established CAD or high risk for CAD.26-28 Fish consumption to achieve an average ingestion of 250 mg/day of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) should be advised in all patients at risk of cardiovascular disease. When a fish oil supplement is used, it should contain both EPA and DHA; a 1-g daily supplement containing 200 to 800 mg of EPA and DHA is a reasonable option.1

◆ Physical activity
Regular exercise has been associated with a significant reduction (20%) in cardiovascular mortality and a trend toward a reduction in myocardial infarction in secondary prevention.29 The benefits of regular exercise are varied and are mostly due to weight reduction, lipid lowering, blood pressure reduction, and type 2 diabetes mellitus prevention. Symptom-limited exercise testing should be performed in patients with CAD before they engage in an exercise program, and high-risk patients should attend a medically supervised facility in which their symptoms can be detected and treated.

As a general recommendation, most patients should perform exercise for a minimum of 30 minutes per day—preferably daily, but at least five days per week. Exercise should involve moderately intensive aerobic activity (eg, walking), with a target heart rate of 60%-75% of maximal heart rate. An increase in daily lifestyle activities (gardening, climbing stairways, etc) should also be encouraged.

◆ Alcohol consumption
People who consume one or two alcoholic drinks daily have a lower mortality risk than those who drink more alcohol than this or drink no alcohol at all. In one pooled estimate involving five prospective cohort studies, total mortality was reduced by 20% in those who drank small to moderate amounts of alcohol compared with nondrinkers.30 So, moderate ingestion of alcohol is recommended for people who drink alcohol regularly.

◆ Weight reduction
Obesity, and especially central or abdominal obesity, is associated with an increased risk of cardiovascular disease. Obesity contributes to hypertension, dyslipidemia, and insulin resistance, which could explain the increment in mortality observed.31 All patients with cardiovascular disease should undergo measurement of waist circumference and calculation of their body mass index. A body mass index of between 18.5 and 24.9 kg/m² should be obtained.1 In patients with an increased waist circumference, the metabolic syndrome should be excluded, and if present, it should be treated. Diet, exercise, and drugs should be used to obtain weight reduction, with an initial target of a 10% reduction in body weight.

Metabolic syndrome
Patients with central or abdominal obesity (ie, a waist circumference over 102 cm in men or over 88 cm in women), hypertension, low HDL cholesterol, elevated triglycerides, and elevated glucose levels have insulin resistance and a high risk of cardiovascular disease. Diagnosis of the metabolic syndrome is made when three or more (out of the five) factors are present. All patients with the metabolic syndrome must be treated aggressively in order to reduce the associated cardiovascular risk.

Other therapies
It has been shown that some drugs have added benefits for patients with cardiovascular disease. Some of these must be recommended to all patients unless there is contraindication (aspirin), whereas others (∝-blockers, clopidogrel, etc.) should be recommended only in some subsets of patients.
NEW INSIGHTS INTO \( I_{1} \) INHIBITION: FROM ISCHEMIA PREVENTION TO IMPROVEMENT IN CORONARY OUTCOMES

◆ Aspirin

Long-term aspirin therapy can reduce myocardial infarction, stroke, and vascular death in patients with different manifestations of prior cardiovascular disease.\(^{31}\) A low dose of aspirin (75-150 mg/day) is recommended, since in an indirect comparison, it was found to attain the same antiplatelet effects as a medium dose (150-325 mg/day) but with a lower risk of gastrointestinal bleeding, although this has not been confirmed by other authors.\(^{32}\) Aspirin can reduce subsequent cardiovascular events by approximately 25%.\(^{33}\) Current guidelines recommend indefinite treatment with oral aspirin (75-325 mg/day) in patients with cardiovascular disease.

◆ \( \beta \)-Blockers

\( \beta \)-Blockers improve survival in patients with myocardial infarction, especially in those with decreased left ventricular systolic function. Therefore, unless contraindicated, \( \beta \)-blockers must be given to all patients with myocardial infarction and left ventricular systolic dysfunction.\(^{34}\) In the prethrombolysis era, several trials showed a mortality benefit of 10% to 15% in patients treated with \( \beta \)-blockers such as propranolol, metoprolol, or atenolol.\(^{35}\) The benefits of \( \beta \)-blockade have also been confirmed in the reperfusion era with up to a 40% reduction in mortality in those with ST-segment elevation or non-ST-segment elevation myocardial infarction.\(^{36}\)

◆ ACE inhibitors and angiotensin receptor blockers

ACE inhibitors have been shown to reduce cardiovascular complications in stable CAD patients. Indeed, based on the evidence obtained from HOPE (ramipril) and EUROPAL (perindopril),\(^{37,38}\) ACE inhibitors have become guideline-recommended treatment for stable CAD patients.\(^{39}\) In addition, ACE inhibitors and ARBs reduce cardiovascular morbidity and mortality in patients with myocardial infarction and left ventricular systolic dysfunction.\(^{1}\) Several ACE inhibitors (for example, enalapril, captopril, ramipril, perindopril) have demonstrated efficacy in such patients. ACE inhibitors are recommended in all myocardial infarction patients who do not fall into the lower risk category defined as those with a normal left ventricular ejection fraction, well-controlled cardiovascular risk factors, and those having undergone a revascularization procedure. For these lower risk patients, ACE inhibitor therapy is also considered reasonable, however. ARBs are recommended in patients who are intolerant to ACE inhibitors and have clinical or radiological signs of heart failure, a left ventricular ejection fraction <40%, or hypertension. In patients with diabetes, ACE inhibitors and ARBs are particularly recommended, as they can diminish the speed of renal function deterioration.

Several subgroup analyses of major cardiovascular trials have suggested that ACE inhibitors and ARBs can reduce the rate of new-onset diabetes by about 25%, although a prospective trial aimed at analyzing this issue (DREAM) failed to confirm the observation.\(^{39}\) There is some evidence that in high-risk patients, such as those with previous myocardial infarction, certain ACE inhibitors reduce cardiovascular mortality beyond the reduction associated with blood pressure reduction,\(^{40,41}\) although for ARBs, this is a matter of some controversy following publication of the results of two recent large-scale trials, ONTARGET and TRANSCEND.\(^{39,40}\) ACE inhibitors should be used first line for the treatment of hypertension in patients with cardiovascular disease; in the case of intolerance to ACE inhibitors, ARBs can also be used first line.

◆ Clopidogrel and warfarin

Clopidogrel is an antiplatelet drug that can be helpful in patients intolerant to aspirin or those who are resistant to it. Furthermore, some trials have shown that the addition of clopidogrel to aspirin can be useful in some high-risk patients with cardiovascular disease, especially those with acute coronary syndromes or who are within 1 year of these events. Patients with peripheral vascular disease and stroke can also attain benefit from this drug.\(^{42}\) Patients who undergo coronary stent implantation should be on combination therapy for several months—especially patients with drug eluting stents, for whom a period of at least 12 months is recommended. Warfarin is only recommended in rare cases in which the patient cannot tolerate aspirin or clopidogrel or when there are specific indications (atrial fibrillation, thrombus, or embolic events).

The international normalized ratio (INR) in these cases should be 2.5-3.5. When associated with aspirin and clopidogrel, the risk of bleeding is increased.\(^{43}\)

◆ Influenza vaccination

Influenza vaccination is currently recommended in all patients with CAD, as influenza infection can produce some complications in patients with known cardiovascular disease, and some trials have shown a reduction in cardiovascular events in such patients as a result of influenza vaccination.\(^{44}\)

New insights: heart rate control with ivabradine

Since the publication of the last guidelines on secondary prevention in CAD, new data has emerged that bears the potential to further improve secondary cardiovascular prevention. In BEAUTIFUL (mORbid- mortality EvAluaTion of the I\(_{1}\) inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction),\(^{45}\) investigators aimed to reduce the heart rate of patients with stable CAD already treated with up-to-date secondary prevention drugs and strategies, and to investigate the effects of this heart rate reduction.

Elevated heart rate is a risk factor for total and cardiovascular mortality in a wide range of populations including the general population, hypertensives, and CAD patients. Even recently in the Losartan Intervention For Endpoint reduction in hypertension (LIFE) trial, a heart rate higher than 84 beats per minute (bpm) was found to be linked to a 61% increase in the risk of development of new-onset atrial fibrillation in hypertensive patients.\(^{46}\)
Heart rate is one of the major determinants of myocardial oxygen consumption, and as a consequence, heart rate reduction is one of the cornerstones of angina prevention and treatment. In a long-term follow-up study in treated stable CAD patients, Diez et al found that those patients with a higher heart rate had significantly higher mortality. In the placebo arm of BEAUTIFUL, cardiovascular outcomes were compared in 2693 patients with a heart rate of ≥70 bpm and in 2745 patients with a heart rate <70 bpm. For every 5-bpm increase, there were significant increases in cardiovascular death (8%), admission to hospital for heart failure (16%), and coronary revascularization (8%). However, evidence for the benefit of heart rate reduction in patients with stable CAD was not available until recently, when the results of BEAUTIFUL were published.

In BEAUTIFUL, over 10,000 patients with CAD and left ventricular dysfunction were randomized either to ivabradine or placebo on top of standard treatment, which included β-blockers in almost 90% of cases. Despite the fact that ivabradine was unable to show any significant effect on the composite primary end point of the trial due to its lack of effect on heart failure events—the major determinants of morbidity and mortality in this high-risk population—several important conclusions can be drawn from this trial. First, in the placebo arm, a significant increase in risk was observed in patients whose heart rate remained higher than 70 bpm, which helped establish a clinical target for the treatment of these patients. Second, in the subset of patients with a heart rate ≥70 bpm who received treatment with ivabradine, a significant reduction in ischemic events was observed (Figure). Thus ivabradine is an anti-ischemic drug able to improve prognosis in this high-risk stable CAD population.

Obviously, this information strengthens the role of ivabradine, although we will have to wait for the next set of new guidelines to see how this is reflected in its placement within the guidelines. For the time being, I think that this new information tells us that patients with CAD and left ventricular dysfunction whose heart rate is above 70 bpm appear to obtain some clinical benefit when their heart rate is decreased with ivabradine on top of β-blockers; they should therefore probably also be treated with ivabradine to reduce ischemic events when the dose of β-blocker cannot be increased further. Given that in BEAUTIFUL the benefits were mainly driven by coronary events and not heart failure complications, it may be reasonable to extrapolate these results to all patients with CAD until further information is gathered.

**Conclusion**

Despite the fact that numerous measures can be taken to decrease the mortality and morbidity of patients with established CAD or those at high risk of developing it, the major problem currently stems from the lack of application of these measures in a large number of patients. In the Euro Heart Survey, only a minority of patients is currently receiving treatment and achieving the recommended targets. It is thus necessary to take steps to improve application of these already established measures and to further expand our knowledge of the subject with new scientific information. Otherwise, the global burden of cardiovascular disease will continue to rise.

---

**References**

10. Chobanian AV, Bakris GL, Black HR, et al; National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treat-
NEW INSIGHTS INTO IFI INHIBITION: FROM ISCHEMIA PREVENTION TO IMPROVEMENT IN CORONARY OUTCOMES

Keywords: stable coronary artery disease; cardiovascular complication; secondary prevention; risk factor; modification; lifestyle; heart rate; antihypertensive; ibabradine

Optimizing secondary prevention treatment in stable coronary artery disease – Radial
La maladie coronaire (MC) stable est un important problème de santé dans le monde entier. Les patients coronariens stables ont un risque élevé de développer des complications cardio-vasculaires ultérieures dont la mortalité est élevée ; des mesures préventives efficaces contre de telles complications sont donc nécessaires. La réduction du cholestérol chez virtuellement tous les patients et la réduction si nécessaire de la pression artérielle sont les facteurs clés du contrôle des facteurs de risque cardio-vasculaire, outil principal de l’amélioration du pronostic de ces patients. Le tabagisme devrait de plus être évité chez tous les patients, un contrôle glycémique sévère devant être maintenu chez les diabétiques. Certains médicaments (comme les antiagrégants plaquettaires, les β-bloquants, les inhibiteurs de l’enzyme de conversion de l’angiotensine) peuvent par la suite améliorer le pronostic chez tout ou partie des coronariens stables. Malgré toutes ces mesures, comme l’étude BEAUTIFUL (morBidity-mortality EvAluTa-tion of the Iβ inhibitor ivabradine in patients with coronary disease and left ventricULar dysfunction) l’a démontré, de nombreux coronariens stables restent toujours à haut risque à cause d’une fréquence cardiaque élevée, déterminant principal de la demande en oxygène du myocarde. Chez ces patients atteints de MC et de dysfonction ventriculaire gauche, l’utilisation d’ivabradine en plus d’un traitement préventif optimal a réduit de façon significative les complications ischémiques telles que la revascularisation et l’infarctus du myocarde, sans cependant influer sur les complications concernant l’insuffisance cardiaque. Puisque de nombreux patients coronariens stables restent à risque à cause d’une fréquence cardiaque élevée (plus de 70 bpm) malgré leur traitement actuel, l’ivabradine peut aider à améliorer leur pronostic cardio-vasculaire ultérieur.
Heart rate reduction is becoming an increasingly recognized therapeutic goal in its own right, supported over the past decade by a steadily growing number of studies reporting on the importance of heart rate with regard to cardiovascular and all-cause mortality. How have recent findings influenced the extent to which you monitor heart rate reduction in coronary patients in daily practice, and what impact has this had on your management of this group of patients?
Cardiovascular practice in the Middle East has, over the last two decades, made great leaps in terms of both quality and access. Its greatest challenge is diabetic atherosclerosis. Angina accounts for over 40% of outpatient clinic volume and despite expensive polypharmacy many such patients remain symptomatic.

Recent epidemiologic studies have confirmed that resting heart rate is an independent predictor of cardiovascular and all-cause mortality in both sexes with and without documented cardiovascular disease. A relatively high heart rate accelerates the progression of coronary atherosclerosis, increases the incidence of myocardial ischemia and ventricular arrhythmia, and impairs left ventricular function. Various studies have documented a continuous increase in risk with heart rates above 60 beats per minute (bpm). Given this evidence of the role played by heart rate, it is not surprising that a number of observational studies should have confirmed the benefits of heart rate reduction. Clinical trial data suggest that heart rate reduction itself is an important mechanism of benefit of heart rate–lowering drugs used after acute myocardial infarction, in chronic heart failure, and in stable angina. An optimal heart rate may be difficult to determine for a given individual, but it seems desirable to maintain resting heart rate substantially below the traditionally defined tachycardia threshold of 90 or 100 bpm.

Despite the availability of \(\beta\)-blockers and calcium channel blockers, we had always suspected that heart rates in our patients with angina or heart failure were suboptimal. To test this suspicion, in July-August 2007 we performed a multicenter cross-sectional study of resting heart rate, measured by palpation, in an outpatient population with stable coronary artery disease and/or heart failure selected by cluster sampling, and assessed the association between resting heart rate and ongoing therapeutic management strategies for cardiovascular events.

The findings consolidated our previous impression that uncontrolled heart rate is very common in this important outpatient cardiology population (Table). This applied equally to patients already treated with other heart rate–lowering agents.

Linear regression identified various predictors of heart rate uncontrolability, including previous hospitalization for congestive heart failure, systolic and diastolic blood pressure, age, severity of angina, and angiographic coronary artery disease. Stable patients with coronary artery disease and/or congestive heart failure receiving guideline-recommended treatment continue to exhibit inadequate control of resting heart rate. This observation offers an undoubted window of opportunity for considering recent advances in heart rate modulation such as \(\beta\) inhibitors.

### Table. Demographic correlates (%) of heart rate (HR).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HR ≤70 bpm</th>
<th>HR &gt;70 bpm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;49</td>
<td>23</td>
<td>76</td>
</tr>
<tr>
<td>49-56</td>
<td>23</td>
<td>77</td>
</tr>
<tr>
<td>56-65</td>
<td>24</td>
<td>76</td>
</tr>
<tr>
<td>&gt;65</td>
<td>25</td>
<td>75</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>25</td>
<td>75</td>
</tr>
<tr>
<td>Female</td>
<td>18</td>
<td>82</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>24</td>
<td>76</td>
</tr>
<tr>
<td>Former</td>
<td>28</td>
<td>72</td>
</tr>
<tr>
<td>Current</td>
<td>16</td>
<td>84</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>23</td>
<td>77</td>
</tr>
<tr>
<td>No</td>
<td>21</td>
<td>79</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>28</td>
<td>72</td>
</tr>
<tr>
<td>Type 1</td>
<td>18</td>
<td>83</td>
</tr>
<tr>
<td>Type 2</td>
<td>19</td>
<td>81</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>23</td>
<td>77</td>
</tr>
<tr>
<td>No</td>
<td>30</td>
<td>70</td>
</tr>
</tbody>
</table>

Despite the availability of \(\beta\)-blockers and calcium channel blockers, we had always suspected that heart rates in our patients with angina or heart failure were suboptimal. To test this suspicion, in July-August 2007 we performed a multicenter cross-sectional study of resting heart rate, measured by palpation, in an outpatient population with stable coronary artery disease and/or heart failure selected by cluster sampling, and assessed the association between resting heart rate and ongoing therapeutic management strategies for cardiovascular events.

The findings consolidated our previous impression that uncontrolled heart rate is very common in this important outpatient cardiology population (Table). This applied equally to patients already treated with other heart rate–lowering agents. Linear regression identified various predictors of heart rate uncontrolability, including previous hospitalization for congestive heart failure, systolic and diastolic blood pressure, age, severity of angina, and angiographic coronary artery disease.

Stable patients with coronary artery disease and/or congestive heart failure receiving guideline-recommended treatment continue to exhibit inadequate control of resting heart rate. This observation offers an undoubted window of opportunity for considering recent advances in heart rate modulation such as \(\beta\) inhibitors.

### Further reading

3. Eagle KA, Lm MG, Dabbous DH. A validated prediction model for all forms of acute coronary syndrome estimating the risk of 6-month post discharge death in an international registry. JAMA. 2004;291:2727-2733.
Heart rate (HR), blood pressure, temperature, and respiratory rate are traditionally considered “vital signs” in the clinical history. High blood pressure was upgraded to “risk factor” status decades ago, and has now been joined by elevated HR as a potential therapeutic target in its own right. Resting HR is a known independent predictor of outcome in cardiovascular patients and the general population. Clinical trial data suggest that HR reduction is the principal mechanism of β-blocker benefit. The pathophysiological explanation is that a fast HR reflects high sympathetic tone and favors coronary atherosclerosis, myocardial ischemia, cardiac hypertrophy, and ventricular arrhythmias. Nevertheless, this has not translated fully into the management of coronary disease. Although most doctors intuitively consider faster HR as an ominous prognostic sign, and take a slow HR to indicate a lesser likelihood of angina and/or a correct β-blocker dosage, few manage HR as a risk factor on a par with cholesterol, blood pressure, etc., checking it regularly, titrating specific treatment, and monitoring long-term response. Yet HR is simplicity itself to measure, from the pulse or electrocardiogram, and is available at every visit.

This simple and powerful prognostic index has not yet entered clinical routine mainly because of the difficulty in defining optimal HR in a given individual. Recent subanalysis of BEAUTIFUL (morBidity-mortality EvAlUaTion of the i,nhibitor ivabradine patients with coronary disease and left ventricular dysfunction) in patients with stable coronary disease, left ventricular dysfunction, and excellent evidence-based background therapy showed that in its own right, an initial HR ≥70 beats per minute—irrespective of cause, treatment, or clinical situation—markedly increases the risk of cardiovascular complications, whether related to myocardial ischemia or heart failure progression.

BEAUTIFUL showed how the HR risk factor can be effectively prevented with ivabradine, a drug that specifically lowers HR by inhibiting the f-channel controlling sinus node discharge. In 5,392 patients with initial HR ≥70 bpm (mean=79 bpm), HR fell to 66 bpm at 24 months on ivabradine (n=2699; mean dose, 6.6 mg twice daily) and 73 bpm on placebo (n=2693). Versus placebo, moderate HR slowing with ivabradine was associated with 22% reduction in coronary outcomes (acute myocardial infarction or unstable angina), 36% reduction in hospital admissions for fatal or nonfatal acute coronary syndromes, and 30% reduction in coronary revascularizations. However, heart failure outcome (hospitalization for emergent or worsening heart failure) did not differ from placebo.

The two goals in treating coronary disease are to relieve angina and prevent acute complications. Antianginal drugs and revascularization achieve the first goal; for the second, several-evidence-based cardioprotective measures are available: diet and weight control, exercise, antiplatelet therapy, statins, and adrenergic and angiotensin inhibitors. As a proven antianginal that protects against the complications of cardiac ischemia in patients with elevated HR, ivabradine helps to achieve both goals.

More specific comments elicited by this Controversial Question include: (i) persistent reluctance about accepting HR as a risk factor and therapeutic target is due to inertia over translating clinical trial results into practice; (ii) elevated HR should be considered a risk factor in its own right and not just an indicator of stress or inadequate β-blocker dosage; (iii) HR should be measured regularly, treated if elevated, and monitored in follow-up visits; and (iv) ivabradine should be upgraded from a second-line antianginal to an evidence-based treatment for preventing ischemic events in coronary patients with basal HR ≥70 bpm.

Personally, I record HR in every inpatient and outpatient, but the BEAUTIFUL results have encouraged me to check this prognostic parameter more strictly still and keep it as low as possible in my coronary patients.

References
CONTROVERSIAL QUESTION

3. P. Brugada and L. Capulzini, Belgium

It is no secret that the pulse has held a major role in the history of medicine. With a little effort we can imagine a relationship between the fantastic descriptions of the pulse from the past and the scientific data from recent clinical trials. Ancient Chinese and Indian medicine assigned great emphasis to study of the pulse. Even today, Tibetan doctors consider analysis of the pulse the first and essential step in approaching a disease, with questions to the patient as only a second step. Well into the 18th century many European universities had chairs entitled De pulsibus et urinis, testifying to the fact that clinical evidence derived from “flowing blood” was increasingly associated with disease of the heart and vessels and with apparently unrelated organs as well.

In the last two decades, epidemiological studies with long-term follow-up have addressed the importance of heart rate (HR) in healthy humans. The association between resting HR and all-cause and cardiovascular mortality is observed in hypertension, metabolic syndrome, and coronary artery disease (CAD). Moreover, after adjusting for other atherosclerosis risk factors, an independent association between baseline HR and all-cause and/or cardiovascular mortality applies in both sexes, especially in subjects with previous myocardial infarction and/or heart failure. Yet elevated HR has remained a neglected cardiovascular risk factor. Only now is it being considered an essential noninvasive index of prognostic stratification in postmyocardial infarction and heart failure.

Elevated HR plays a major role in CAD, not only as a trigger of ischemic episodes but also as a significant predictor of cardiovascular morbidity and mortality. HR is a primary determinant of myocardial oxygen demand and may also affect myocardial perfusion. This mechanism is the primary basis for the anti-ischemic and antianginal effects of heart rate-lowering drugs. HR lowering also increases coronary blood flow, hence myocardial oxygen supply, mitigating ischemia by increasing diastolic perfusion time. In theory, the disruption of atherosclerotic plaques is partly due to mechanical perturbation of the plaque by the foreshortening and twisting of large epicardial arteries during systole, which is diminished by HR lowering. In agreement with many epidemiological studies, substantially increased risk is observed at lowish heart rates of 70-80 beats per minute (bpm). Several trials have retrospectively shown that reduced heart rate accounts for the benefits of β-blockers and nondihydropyridine calcium channel blockers in CAD and heart failure. BEAUTIFUL (morBidity–mortality EvAlUaTion of the If inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction) and its subanalyses point in the same direction: HR reduction on ivabradine improved coronary outcome in stable CAD patients with HR ≥70 bpm, even on top of best-practice therapy.

Thus, assuming a linear relationship between resting HR and clinical outcome in CAD, we can argue that “slower is better,” although a specific target rate beyond which further HR reduction should be considered unwarranted has still to be defined.

In summary, the evidence indicates that resting HR is a strong independent predictor of cardiovascular morbidity and mortality in CAD. We cannot therefore afford to ignore HR monitoring in our day-to-day management of such patients. The pulse is one of the simplest parameters to measure, with even a single casual value being a strong predictor of events if based on good number of cardiac cycles. In addition, in ivabradine, a novel selective agent that selectively inhibits the If pace-maker current in the sinoatrial node, we have an agent that makes HR lowering a readily attainable pharmacological target in CAD patients, even when cotreated or with the classical contraindications to β-blockers and/or calcium channel antagonists such as atroventricular conduction disturbances, bronchial spasm, and severe peripheral arterial disease.
Adequate heart rate control by a single agent may be impossible and require additional agents. The recent ASSOCIATE study (Antianginal efficacy and Safety of the aSSociation Of the I blockers, Current inhibitor Ivabradine with a beTa-blockEr) showed that additional blockade of the I blockers and ivabradine was effective in patients with chronic stable angina already receiving β-blockers. Although not explicitly tested, the use of rate-lowering agents to improve prognosis after myocardial infarction may increase the pressure on cardiologists to achieve adequate rate reduction. The evidence is perhaps less compelling in heart failure, which therapeutically is also somewhat more complex, but there are some grounds at least for assessing heart rate response in this group too.

Since the response to any drug is individual, monitoring heart rate response to drugs with rate reduction as their major or one of their major effects offers an easy way to assess drug efficacy in an individual. Finally, although the evidence suggests that rate reduction benefits all patients at risk of cardiovascular disease, it is strongest for those with rates >70 bpm, as observed in BEAUTIFUL (morBidity-mortality EvAluatIon of the I inhibitor IvabrAdine in patients with coronary disease and left ventricular dysfunction). This requires further evaluation and consideration of issues such as which heart rate to measure (basal, mean 24-hour, peak exercise, recovery exercise), whether the evidence is equally applicable to women, and the fact that existing information relates to sinus rhythm. The availability of drugs such as ivabradine that lower heart rate as their principal pharmacodynamic effect offers the exciting potential of definitive answers to many outstanding questions regarding the role of rate reduction in cardiological practice.

References
Since the beginning of time, man has viewed the characteristics of the pulse as pointers to health, disease, and death. Ancient Chinese doctors were responsible for the first written reference to the pulse as a diagnostic tool in around 500 BC. Indeed it was the single most important tool at their disposal. Patients would extend their arm through a bedside curtain for the physician to determine the symptoms, diagnosis, prognosis, and proper treatment by intensive palpation of the pulse. Literally hundreds of possible characteristics were obtainable, since the pulse had three distinct divisions, each associated with a specific organ, and each division had a separate quality, of which there were dozens of varieties. Examination even took into consideration the hour, day, and season of the year. It was thus hardly surprising that the Muo-Ching textbook should have devoted its 10 volumes exclusively to details of the pulse.1

Many studies have described the major prognostic impact of heart rate. For example, the Coronary Artery Surgery Study (CASS) of 24,913 patients with suspected or proven coronary artery disease showed an association between heart rate exceeding 83 beats per minute and increased cardiovascular mortality.2 Similarly, the more recently published INternational VErapamil SR-trandolapril STudy (INVEST) in 22,573 patients with coronary artery disease and hypertension found an association between heart rate exceeding >75 beats per minute and increased cardiovascular events.3

Ivabradine is the first drug to show a specific impact on heart rate thanks to a unique mechanism of action: inhibition of the sinus node I(f) current. It has recently been shown to reduce angina frequency and increase total exercise duration and time to 1-mm ST-segment depression in stable coronary artery disease.4,5 In addition, in stable coronary artery disease and left ventricular systolic dysfunction, it was found to lower the incidence of cardiovascular events in the patient subgroup with heart rates of 70 beats per minute or over.6

Evaluation of the pulse has thus been used for thousands of years in the evaluation of patients. Perhaps denigrated as a clinical parameter in the modern era on the grounds of its sheer accessibility and simplicity, we now have incontrovertible epidemiological evidence that heart rate is an important prognostic factor, in particular when it exceeds 70 beats per minute. Ivabradine modulates heart rate in a specific way that accounts for its compatibility with a wide range of standard anti-ischemic therapies. It is thus becoming established as a useful addition to the pharmaceutical armamentarium, providing positive prognostic impact in patients with stable coronary disease and left ventricular systolic dysfunction. The challenge this question raises for cardiologists in 2009 is therefore: have you incorporated the monitoring and, as appropriate, the modulation of heart rate into your day-to-day management of coronary patients?

References
Relieving the symptoms of angina and improving quality of life and functional status are the key goals in managing patients with coronary artery disease. But as well as looking after the blood pressure and cholesterol levels of their coronary patients, physicians should also monitor their heart rates. There are many reasons for doing so. First, we know heart rate to be one of the most important determinants of myocardial oxygen demand: a high heart rate induces or exacerbates myocardial ischemia because it increases myocardial oxygen demand at the same time as it decreases myocardial perfusion, in the latter case by shortening the duration of diastole. Second, there is an association between reduced heart rate and the growth of collateral vessels in coronary patients. The third reason is that resting and peak exercise heart rate may be predictive of cardiovascular and coronary mortality. For these reasons, reducing the heart rate is becoming an increasingly recognized therapeutic goal in its own right. In our own department, heart rate reduction has been a therapeutic goal in our routine management of angina for many years.

Subanalysis of BEAUTIFUL (morBidity-mortality EvAIUaTion of the I, inhibitor ivabradine in patients with coronary disease and left ventricUlar dysfunction) demonstrated that elevated heart rate is a strong independent risk factor in patients with coronary artery disease and left ventricular dysfunction, even in those receiving best-practice background treatment, including with β-blockers. These results extend those of previous observations to a wide range of coronary events such as admission to hospital for fatal and nonfatal myocardial infarction, as well as coronary revascularization. They suggest that coronary patients with a heart rate above 70 beats per minute, who form the majority of the coronary population in clinical practice, are at excess risk of all cardiovascular events and death. Hence the importance of heart rate monitoring and, as appropriate, modulation in the management of coronary artery disease.

Although resting heart rate independently predicts coronary events in men, the evidence to date suggests that this relationship is weaker or absent in women. However, according to a recently published study, women with a resting heart rate exceeding 76 beats per minute are 1.6 times more likely to develop cardiovascular events; the association is reported to be stronger in younger postmenopausal women. These women have higher levels of body weight, blood pressure, and cholesterol. Women with the highest heart rates were also more likely to develop diabetes, smoke, and suffer from depression. In other words, a higher heart rate is beginning to appear a bona fide risk factor for cardiovascular disease in women.

Heart rate should be assessed as a prognostic marker and as a guide to optimal medical treatment in men and also in women. Now that recent clinical trials have clearly shown both the importance of higher heart rates and the benefits of heart rate reduction, we should use heart rate reduction strategies in our daily practice more than in the past. Patients with stable angina, a low ejection fraction, and an elevated heart rate are the best candidates for combined heart rate reduction strategies. However, we need new data and evidence to generalize this recommendation to all coronary patients.

References
To what extent has monitoring of HR reduction become part of your coronary daily practice?

In patients with symptomatic coronary artery disease, heart rate has yet to become an established treatment target in daily cardiology practice, unless clinical signs, symptoms, and consequences of supraventricular or ventricular tachycardia are present. Heart rate reduction is rarely considered in asymptomatic patients with sinus rhythm of 80 beats per minute (bpm). Currently we often fail to take slightly elevated heart rate into consideration when evaluating our patients in a clinical setting. Yet we act appropriately when the issue is made explicit, as shown by the responses to two simple scenarios that I present in my lectures. In the first, I invite students to choose which of three cyclists, with resting heart rates of 60, 80, and 100 bpm, respectively, is most likely to win a race to the summit of Mont Ventoux. The cyclist with the lowest resting heart rate is invariably chosen. The second scenario asks which of three patients in the emergency room, with heart rates of 60, 80, and 100 bpm, respectively, requires the most immediate medical care. The patient with the highest heart rate is always chosen.

Studies showing a relationship between heart rate and prognosis are already some three decades old. The strong relationship applies in healthy subjects as well as in patients. More recent data show an association between elevated resting heart rate and increased cardiovascular mortality and overall mortality. Careful statistical analysis has shown the association to be independent of other risk factors and not merely an epiphenomenon caused, for instance, by underlying disease that elevates heart rate.

How should these results impact our daily practice? Optimal β-blocker treatment is currently defined by a resting heart rate of 60 bpm. However, β-blockers also have other valuable autonomic effects. Does this make heart rate reduction less important? Selective (or pure) heart rate reduction by ivabradine only reduces the heart rate. It has no effects on myocardial contractility, blood pressure, or the central nervous system. Thus any clinical benefit for the patient is due to heart rate reduction per se.

BEAUTIFUL (morBidity-mortality EvAlUaTion of the l, inhibitor ivabradine in patients with coronary disease and left ventricu-Lar dysfunction) was the first study to establish this relationship prospectively, showing an elevated resting heart rate ≥70 bpm to be an independent risk factor for several major cardiovascular events. The explanation for its mode of action is simple: a slower heart rate requires less energy in systole and allows longer for recovery.

BEAUTIFUL reported a neutral effect on the primary composite end point. Most end points were heart failure–driven in this patient group with a left ventricular ejection fraction of 0.32. Other major factors uninfluenced by pure heart rate reduction determine prognosis in such patients. When coronary end points are evaluated in patients at risk (resting heart rate ≥70 bpm), ivabradine reduces both myocardial infarction and coronary revascularization. This makes elevated heart rate a key therapeutic target in coronary patients.

The study results did not answer all questions. We should aim for lower heart rate in our patients. This is poorly tolerated using β-blockers alone—those advocating such therapy should try it for themselves! In medicine it takes time to establish and win acceptance for a new clinical treatment in daily practice. It took over 15 years to bring angiotensin-converting enzyme inhibition into the routine management of heart failure patients. Hopefully the concept of pure heart rate reduction will take less time as the upcoming study data become available.
Although the importance of resting heart rate as an independent predictor of cardiovascular morbidity and mortality is not yet generally perceived, strong evidence supports its role not only in coronary artery disease, but also in patients with cardiovascular risk factors and heart failure, and in the general population. An elevated heart rate does not simply favor the progression of atherosclerosis and development of cardiovascular disease and clinical events; heart rate lowering also correlates with clinical benefit. Pathophysiological studies have shown that elevated resting heart rate is directly and independently related to the extent and progression of atherosclerosis via several mechanisms. High heart rate increases the amplitude and frequency of tensile stress on the arterial wall, prolongs coronary endothelial exposure to systolic low and oscillatory shear stress, favors endothelial dysfunction, and increases pulsatile arterial load on the heart. Not only does it promote atherosclerosis, it also accelerates weakening of the fibrous cap, ultimately increasing the risk of plaque rupture and acute coronary events. Elevated heart rate is common in diabetes, altered glucose metabolism, and metabolic syndrome. Since most patients with cardiovascular risk factors and/or cardiovascular disease have different degrees of altered glucose and insulin metabolism, elevated heart rate is often associated with a shift from glucose to free fatty acid oxidation, which in turn further reduces myocardial energy production. Thus elevated heart rate impacts the cardiovascular system via dual effects on hemodynamics and cardiac metabolism.

The need to control heart rate became evident after the Coronary Artery Surgery Study (CASS) registry. The International Study of Infarct Survival–1 (ISIS-1) found a significant gain in survival from heart rate reduction in the acute myocardial infarction setting. Thereafter β-blockers became the mainstay of coronary treatment. Since the late 1980s, physicians treating coronary artery disease, in particular those trained in Europe, have viewed a low heart rate as essential (the emphasis has been lower across the Atlantic). Physicians became used to using β-blockers without intrinsic sympathomimetic activity, adjusting the dose to a target heart rate ≤60 beats per minute (bpm). When newer β-blockers came onto the market, the next generation of physicians tended to regard the low heart rate issue as less important.

The therapeutic transformation recently brought by ivabradine has reinstated heart rate control as a therapeutic target and reminded physicians of the prognostic impact of an elevated rate. BEAUTIFUL (morBidity-mortality EvAlUaTion of the I(f) inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction) confirmed that coronary patients with left ventricular dysfunction and heart rate ≥70 bpm are at significantly greater risk of cardiovascular death and hospitalization for fatal and nonfatal myocardial infarction, heart failure, and coronary revascularization. It also showed an association with significant benefit on coronary end points resulting from heart rate reduction with ivabradine in patients with rates ≥70 bpm. This is extremely important as no current anti-ischemic agent has ever been shown to reduce coronary end points. More recently, ivabradine has proven highly effective alone or in combination with β-blockers for controlling myocardial ischemia.

The strong evidence that elevated heart rate has a direct and independent role as a prognostic factor in cardiovascular disease highlights the need for rate control in all patients at cardiovascular risk. Heart rate monitoring and modulation should therefore feature more prominently than ever in our management of these patients.

Further reading
Controversial Question

9. U. Thadani, USA

Epidemiological data suggest a strong association between adverse cardiac outcomes, including increased mortality, and elevated heart rate (HR) in coronary artery disease (CAD) patients and those with ischemic cardiomyopathy due to reduced left ventricular (LV) systolic function. β-Blockers reduce cardiac mortality and morbidity in patients with acute myocardial infarction (MI), unstable angina, and dilated cardiomyopathy. It has been proposed that the HR-reducing effect of β-blockers is responsible for improved clinical outcomes in these patients.

Substantial data show that in patients with chronic stable angina, HR-lowering drugs such as β-blockers and the selective I1 current inhibitor, ivabradine, increase angina-free walking time and reduce angina frequency during daily activities and exercise-induced myocardial ischemia. Further improvement in exercise duration and reduction of exercise-induced myocardial ischemia was recently reported when ivabradine was added to atenolol. However, no trials have studied the effects of these HR-lowering drugs in monotherapy on mortality or MI in patients with chronic stable angina and preserved LV function. In a large placebo-controlled study in patients with CAD and LV ejection fraction <40%, the majority of whom were already taking a β-blocker, addition of ivabradine did not reduce the primary composite end point of cardiovascular death or admission for MI or new-onset or worsening heart failure. In a prespecified subgroup with HR >70 bpm, addition of ivabradine did not reduce the primary end point, but did reduce the secondary end points of admission to hospital for fatal and nonfatal MI and coronary revascularization.

In patients with atrial fibrillation (AF), lowering ventricular rate with β-blockers, diltiazem, digoxin, and amiodarone—which slow atrioventricular node conduction—improves symptoms and quality of life.

Based on published data and personal experience over several years, it has been my standard practice to monitor HR and adjust drug dosage to achieve optimal β-blockade in patients with chronic stable angina. My target is to achieve a resting HR of 55-65 beats per minute (bpm), provided the patient is able to tolerate the medication and does not experience increased fatigue, breathlessness, symptomatic hypotension, or other intolerable adverse effects. Since resting HR is influenced by emotional state, physical activity, and many other stimuli, I usually rely on HR in the sitting position obtained over 30-60 seconds, after the patient has rested for 5-10 minutes. HR obtained from an electrocardiogram in the supine position is also useful to exclude high-grade atrioventricular block if the heart rate is <50 bpm. In patients remaining symptomatic despite resting HR of 55-65 bpm, I usually evaluate HR response to exercise to assess the adequacy of β-blockade. My target is a HR of 110-120 bpm during symptom-limited electrocardiogram-monitored treadmill or bicycle exercise stress test.

In patients with dilated cardiomyopathy, I monitor HR primarily to achieve the target dose of β-blocker shown in trials to reduce cardiac mortality and morbidity, rather than specifically to lower it to <70 bpm. This is done over a prolonged period, with special attention paid to any adverse effects that necessitate dose reduction.

In patients with AF with rapid ventricular response, I monitor resting HR as well as HR during daily activities, often with Holter monitoring over a period of 24 hours. My target is <80 bpm at rest and <110 bpm during physical activities.

In conclusion, this approach to monitoring HR has permitted me to optimize pharmacotherapy for patients with chronic stable angina, heart failure, and AF. I am very careful when treating elderly patients not to lower HR below 60-70 bpm, as these patients often take multiple medications, have multiple comorbid conditions, and are prone to postural hypotension symptoms.

References
Clinical benefits of pure heart rate reduction with Procoralan: evidence and perspectives

by I. Elyubaeva, France

Despite many therapeutic advances in the field of cardiology, coronary artery disease (CAD) remains the leading cause of death and disability worldwide. Reduction of elevated resting heart rate is a well-established approach to relieving angina and ischemia, and has long been advocated as a therapeutic approach in the management of cardiovascular disease. A large body of evidence indicates that high resting heart rate is a risk factor for adverse outcomes in a variety of populations. Recent evidence from morbidity-mortality Evaluation of the If inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction (BEAUTIFUL) demonstrated that elevated heart rate (≥70 beats per minute; bpm) increases cardiovascular risk. Procoralan is the only agent to have been approved for clinical practice that has a unique action on cardiac pacemaker activity, based on selective and specific If current inhibition. The clinical efficacy and safety of Procoralan has been demonstrated in comparison with placebo and well-established antianginal drugs such as β-blockers and calcium antagonists. The recent study, evaluation of the Antianginal efficacy and Safety of the association Of the If current inhibitor IvabrAdine with a beTa-blockEr (ASSOCIATE), demonstrated that in patients with stable angina receiving the β-blocker atenolol, Procoralan produced a significant reduction in heart rate and improvement in all exercise capacity parameters. The BEAUTIFUL results suggest that Procoralan could have a role not only in symptomatic treatment, but also in prevention of coronary events in CAD patients with a heart rate ≥70 bpm, over and above routine preventive therapy. Other ongoing trials should provide important evidence and insights that will enhance the care and management of patients with stable CAD or heart failure.

Address for correspondence:
Irina Elyubaeva, Servier International, 35, rue de Verdun, 92284 Suresnes Cedex, France
(e-mail: irina.elyubaeva@fr.netgrs.com)

www.medicographia.com
which can induce or exacerbate myocardial ischemia. Furthermore, experimental data and clinical observations support the notion of the importance of heart rate in the pathophysiology of atherosclerosis and plaque rupture. An elevated heart rate enhances mechanical arterial wall stress and prolongs the exposure of coronary endothelium to systolic low and oscillatory shear stress. All these processes induce structural and functional changes in endothelial cells, which accumulate over time in atherosclerosis-prone regions, promoting atherosclerosis. Moreover, elevated heart rate caused by mechanical stress may promote weakening of the fibrous cap, ultimately increasing the risk of plaque disruption and the onset of an acute coronary syndrome. Elevated resting heart rate has been demonstrated to be a significant predictor of all-cause and cardiovascular mortality in the general population and in patients with cardiovascular disease. Analysis from the Coronary Artery Surgery Study (CASS) involving 24,913 patients with suspected or proven CAD who were followed up for 14.7 years demonstrated that both all-cause and cardiovascular mortality were directly and independently related to resting heart rate at study entry. Patients with resting heart rates of 77 beats per minute (bpm) or above were at an elevated risk of total and cardiovascular mortality after adjustment for other clinical variables. Another retrospective analysis from the randomized controlled INternational VErapamil SR-Trandolapril StUdy (INVEST) in CAD patients with hypertension demonstrated an increased risk of cardiovascular mortality and morbidity with increasing baseline resting heart rate. This association was evident in patients with a baseline heart rate of above 70 bpm. Recently, prospective results from BEAUTIFUL (morBidity-mortality EvaLuation of the iVabradinE in patients with coronary disease and left ventricUlar dysfunc) showed that patients with heart rates of 70 bpm or greater have increased risk of cardiovascular death (34%; \(P=0.0041\)), admission to hospital for heart failure (53%; \(P<0.0001\)), admission to hospital for myocardial infarction (46%; \(P=0.0066\)), and coronary revascularization (38%; \(P=0.037\)). Thus reducing elevated heart rate could reduce the risk of cardiovascular events. Consistent with this understanding of the important role of elevated heart rate in the pathophysiology of CAD, heart rate reduction should clearly be considered as a key therapeutic goal in patients with CAD; the short-term implication is better prevention of ischemia, and the long-term implication is better prevention of cardiovascular events (Figure 1).

For the past few decades, \(\beta\)-blockers have been used widely as effective heart-rate-lowering drugs. However, in addition to heart rate reduction, \(\beta\)-blockers have numerous other cardiac and extra-cardiac effects that may not necessarily be clinically beneficial. Furthermore, recent studies have suggested that after a myocardial infarction, only approximately 60% of patients receive \(\beta\)-blockers. Thus specific heart-rate-lowering agents that could be used with or without \(\beta\)-blockers could be clinically useful. Procoralan (ivabradine) is a selective heart-rate-lowering agent that acts by inhibiting the pacemaker ionic current \(I_f\) in sinoatrial node cells. At therapeutic concentrations, Procoralan acts by selectively and specifically binding to \(I_f\)-channels to inhibit the \(I_f\) current in a dose-dependent manner, with no effects on other cardiac ionic currents.

Hence, in contrast with \(\beta\)-blockade, selective heart rate reduction with Procoralan preserves myocardial contractility, isovolumic ventricular relaxation, and coronary vasodilation, and therefore ensures the full benefits of prolonged diastole on coronary blood flow supply. Thus in addition to lowering myocardial oxygen demand, Procoralan increases diastolic perfusion time and improves oxygen supply while preserving...
cardiac stroke volume at rest and during exercise.\textsuperscript{10-12} These pharmacological effects translate into tangible clinical advantages in CAD patients.

**Clinical benefits of exclusive heart rate reduction with Procoralan**

The clinical development program of Procoralan involved patients across various stages of the cardiovascular disease spectrum, with the first phase of the development program being carried out in more than 5000 patients with chronic stable angina pectoris. The program was focused on several international, multicenter, randomized, double-blind, parallel-group trials.

**Antianginal and anti-ischemic efficacy**

The first large-scale study of Procoralan was an international, multicenter, double-blind trial, in which 360 patients with a history of chronic stable angina were randomized to placebo or Procoralan. Procoralan dose-dependently reduced heart rate, which was associated with a significant increase in the time to 1-mm ST-segment depression and time to limiting angina ($P<0.005$). Data from the subsequent open and run-out periods showed that both the antianginal and anti-ischemic benefits of Procoralan persisted without the development of pharmacological tolerance.\textsuperscript{13} These encouraging results compared with placebo supported the rationale for testing Procoralan versus other antianginal anti-ischemic drugs like $\beta$-blockers and calcium channel blockers.\textsuperscript{14,15} The INternational TrIal of the AnTianginal effects of IVabradinE compared with atenolol (INITIATIVE) compared the anti-ischemic and antianginal efficacy of Procoralan 7.5 mg and 10 mg twice daily and atenolol 100 mg once daily in 939 stable angina pectoris patients.\textsuperscript{14} After 4 months of treatment, Procoralan increased total exercise duration by 86.8 seconds, compared with 78.8 seconds for atenolol ($P<0.001$ for non-inferiority). Major improvements were also noted in time to limiting angina (91.8-96.9 seconds vs 85.4 seconds for atenolol; $P<0.001$) and time to angina onset (139.6-145.2 seconds vs 135.2 seconds for atenolol; $P<0.001$). Moreover, the improvement in exercise capacity for each beat of heart rate reduction was greater for Procoralan than atenolol (Figure 2). This difference may be due to the greater anti-ischemic efficiency of the exclusive heart rate reduction with Procoralan. Clinically, this means that patients treated with Procoralan can adapt better to exercise, while also gaining the full benefits of heart rate reduction.

In another comparative study, 1195 stable angina patients received either Procoralan (7.5 mg twice daily or 10 mg twice daily) or amlodipine 10 mg once daily for 3 months.\textsuperscript{15} Time to 1-mm ST-segment depression increased by 45 seconds with Procoralan versus a 40-second increase with amlodipine ($P<0.001$), and both treatments decreased the anginal attack frequency by two-thirds. In addition, Procoralan had a superior effect on the reduction of rate-pressure product (a surrogate marker of myocardial oxygen consumption) compared with amlodipine, and a similar safety profile.

Importantly, the efficacy of Procoralan in reducing heart rate and the frequency of angina was demonstrated across a wide range of populations with stable angina, including the elderly, females, and patients with asthma/chronic obstructive pulmonary disease, making it suitable for most stable coronary patients, including also those with contraindications or an intolerance to $\beta$-blockers.\textsuperscript{16} Analysis of the efficacy of Procoralan in diabetic patients with stable angina indicates that Procoralan retains its antianginal efficacy in diabetic patients and is devoid of the undesirable metabolic effects in diabetics that can be seen with $\beta$-blockers or dihydropyridine calcium channel blockers.\textsuperscript{17}

**Antianginal and anti-ischemic efficacy of Procoralan in combination with $\beta$-blockers**

In routine clinical practice, stable angina patients may not be controlled with one drug alone. Though combination therapy is recommended to improve symptomatic management,\textsuperscript{18} most clinical studies have demonstrated only modest improvement in exercise tolerance test parameters with combination therapy compared with monotherapy at the peak of drug activity, with no significant differences 6 hours after drug intake.\textsuperscript{19}

Recently, the anti-ischemic efficacy of Procoralan in combination with $\beta$-blocker therapy was investigated in a 4-month study of 889 stable angina patients already receiving atenolol 50 mg/day.\textsuperscript{20} This study, ASSOCIATE (evaluation of the Antianginal efficacy and Safety of the assocIation Of the I, Current inhibitoR IvabrAdine with a boTa-blockErs), included patients who had a positive symptom-limited exercise test on atenolol 50 mg once daily. Patients were randomly assigned to treatment with Procoralan 5 mg twice daily uptitrated to 7.5 mg twice daily after 2 months (n=449), or placebo (n=440).
in addition to the β-blocker. In the Procoralan group, 90% of patients were uptitrated to receive 7.5 mg twice daily. The baseline resting heart rate in these patients was 67 bpm. Procoralan reduced the baseline heart rate by 9 bpm at the end of the study, which was associated with a statistically significant improvement in all exercise test parameters recorded at the trough of activity at the end of 4 months. Total exercise duration, which was the primary efficacy criteria, increased threelfold compared with placebo (Figure 3). This study is one of the largest studies of combination therapy for angina pectoris, and the effects achieved were demonstrated at the trough of drug activity, which signifies that the combination works all the time. This study clearly demonstrates that in patients with stable angina receiving the β-blocker atenolol, Procoralan provides a significant improvement in total exercise duration, as demonstrated using the standardized Bruce protocol for exercise testing, in which higher workloads are reached more rapidly than in the modified Bruce protocol. The more demanding standard Bruce protocol was chosen in view of the fact that patients were receiving background therapy known to improve exercise capacity. In terms of the size of the trial, compliance with regulatory recommendations, and the consistency of the significant improvements across all exercise tolerance test criteria and time points, this trial may represent the most compelling demonstration of the benefits of any combination of antianginal drugs published to date.

**The long-term anti-ischemic and antianginal efficacy of Procoralan**

The long-term antianginal efficacy of Procoralan was investigated in a population of 386 stable angina patients, in whom Procoralan 5 mg twice daily or Procoralan 7.5 mg twice daily was added to other therapies. After 12 months, mean heart rate had significantly reduced from baseline by 10 bpm in the Procoralan 5 mg twice daily group, and by 12 bpm in the 7.5 mg twice daily group. The heart rate-lowering efficacy of Procoralan was associated with significant antianginal efficacy. The mean number of angina attacks per week decreased by 50% (P<0.001) with Procoralan. This sustained reduction in angina attack frequency was consistent with that observed in previous controlled studies. Reduction in the frequency of angina attacks in patients who were still symptomatic at inclusion and who were being treated with other antianginal drugs, in whom Procoralan was given as add-on therapy, provided a good representation of the effects of Procoralan under the usual prescribing conditions in clinical practice. The sustained efficacy of Procoralan throughout the study was consistent with the absence of pharmacological tolerance, providing proof that stable coronary patients can be optimally treated with Procoralan over the long term.

**Reduction of coronary events with Procoralan**

The two aims in treating a patient with CAD are to relieve anginal symptoms and to prevent cardiovascular events. The ability of Procoralan to reduce cardiovascular events has been evaluated in BEAUTIFUL. BEAUTIFUL was carried out in 10,917 patients with documented CAD and associated left ventricular systolic dysfunction, and was the first prospective, randomized, controlled study that assessed whether Procoralan reduces cardiovascular events in such patients. Most of the study patients were already receiving guideline-recommended cardiovascular therapy: antiplatelet agents (94%), angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (90%), β-blockers (87%), as well as lipid-lowering agents (76%). The mean heart rate in these patients was 71.6 bpm despite the fact that 87% were on β-blockers, and 50% of the patients had a heart rate above 70 bpm. This baseline heart rate in BEAUTIFUL was similar to that in observational studies in CAD patients. The first important finding from BEAUTIFUL is that patients with an elevated heart rate (>70 bpm) are clearly at a very high risk for cardiovascular events such as myocardial infarction (46% increased risk, P=0.0066), coronary revascularization (38%, P=0.037), or cardiovascular death (34%, P=0.0041).

In the overall study population, treatment with Procoralan did not result in a significant change in the primary composite end point of cardiovascular death, admission to hospital for acute myocardial infarction, and admission to hospital for heart failure. However in a pre-specified subgroup of patients with heart rate ≥70 bpm, treatment with Procoralan resulted in a significant reduction in the composite coronary end point defined as a composite of hospitalization for myocardial infarction (fatal or nonfatal) or unstable angina (relative risk reduction, 22%; P=0.023). In the Procoralan group, there was a significant 36% relative risk reduction in hospitalization for fatal or nonfatal myocardial infarction (Figure 4) (P=0.001) and a 30% reduction in hospitalization for coronary revascularization, which includes percutaneous coronary interventions as well as coronary artery bypass grafts (P=0.016). It is im-

![Figure 3. Changes in total exercise duration from baseline to month 4 among stable angina patients treated with the addition of either Procoralan (5 mg twice daily for 2 months increased to 7.5 mg twice daily for 2 months; n=449) or placebo (n=440) to β-blocker therapy (atenolol 50 mg once daily).](image-url)
The reduction in coronary events with Procoralan could be particularly in CAD patients with a heart rate above 70 bpm, over and above routine preventive therapy. A large proportion of stable angina patients in clinical practice have a resting heart rate above this threshold.27 Considering the emerging role of heart rate reduction as a therapeutic approach in CAD management, it was felt necessary to evaluate the effect of Procoralan in acute coronary syndromes, as well as in CAD patients with documented preserved left ventricular ejection fraction. Evaluation of the Intravenous I1 inhibitor ivabradine after ST-segment elevation

Figure 4. Kaplan-Meier time-to-event plots by treatment group (Procoralan or placebo) in stable coronary artery disease patients with elevated resting heart rate (≥70 beats per minute) for hospitalization for myocardial infarction (Panel A), and coronary revascularization (Panel B).


important to note that these results were obtained when the majority of patients were already receiving currently recommended optimal preventive therapy and that the results emerged in just 2 years of follow-up. BEAUTIFUL is the first demonstration that in coronary patients already receiving optimal preventive therapy, an antianginal drug can reduce the risk of myocardial infarction and revascularization.

How does Procoralan prevent coronary events?
The reduction in coronary events with Procoralan could be explained by its exclusive heart rate reduction, which leads to superior anti-ischemic efficacy,10-12 and the prevention of atherosclerosis development and progression.23,24 The prevention of endothelial dysfunction—the first step in the development of atherosclerosis—was demonstrated with Procoralan in a transgenic model of dyslipidemia and endothelial dysfunction. Three-month treatment with Procoralan preserved the endothelium-mediated vasodilation in the renal and cerebral arteries of mice expressing human apolipoprotein B (apoB-100). Procoralan restored the endothelium-dependent vasodilation in cerebral vessels, whereas in the same animal model, metoprolol did not restore endothelial function to the same degree.23 This was possibly because of inhibitory effects of metoprolol on β-adrenoceptor-mediated activation of endothelial nitric oxide synthase.23,26 Pre-clinical studies have also demonstrated that Procoralan reduces the atherosclerotic plaque size in the aortic root and ascending aorta by 40% and 70%, respectively (P<0.05). Procoralan also markedly reduced vascular oxidative stress, nicotinamide adenine dinucleotide phosphate oxidase activity, superoxide production, and lipid peroxidation.23 These factors could contribute clinically to the prevention of the progression of atherosclerosis. These experiments support the rationale for heart rate reduction with Procoralan as an intervention to improve endothelial function and to attenuate the progression of atherosclerosis and cardiovascular event prevention.

The safety profile of Procoralan
The large clinical development program of Procoralan has provided a solid demonstration of its tolerability. The most frequently encountered adverse events—sinus bradycardia and visual disturbances—are related to the drug’s mechanism of action; ie, inhibition of sinus node f-channels and inhibition of h-channels in retinal rods and cones, though their incidence is low. In BEAUTIFUL, the incidence of symptomatic sinus bradycardia (heart rate <55 bpm) was 3%. In patients with stable angina receiving β-blockers and Procoralan, withdrawal due to sinus bradycardia was 1.1% in the Procoralan group. The rate of visual symptoms (phosphenes, blurred vision, and visual disturbances) was also very low in BEAUTIFUL and led to discontinuation in only 0.5% of patients receiving Procoralan (28 patients) versus 0.2% of patients receiving placebo (9 patients). Importantly, the abrupt discontinuation of Procoralan has not resulted in a rebound angina phenomenon.

Current place of Procoralan in clinical practice and future perspectives
Procoralan is currently recommended in the symptomatic treatment of CAD patients.13 The results of BEAUTIFUL suggest that Procoralan could have a role not only in symptomatic treatment, but also in the prevention of coronary events particularly in CAD patients with a heart rate ≥70 bpm, over and above routine preventive therapy. A large proportion of stable angina patients in clinical practice have a resting heart rate above this threshold.27
mYocardial infarction (VIVIFY) is an ongoing trial that is evaluating the efficacy and safety of Procoralan in patients with acute myocardial infarction with ST-segment-elevation who are undergoing percutaneous coronary intervention. To evaluate the efficacy of heart rate reduction with Procoralan in the reduction of cardiovascular outcomes in stable coronary patients with preserved left ventricular ejection fraction, another morbidity-mortality study has been designed—Study assessing the morbidity-mortality benefits of the i, inhibitor ivabradine in patients with coronary artery disease (SIGNIFY).

In patients with congestive heart failure, heart rate lowering using β-blockers is associated with a reduction in mortality. Pilot studies with Procoralan in patients with moderate left ventricular dysfunction have shown that Procoralan reduced left ventricular end-systolic and end-diastolic volumes, suggesting a preserving effect on cardiac function.

These results have formed the basis of the Systolic Heart failure with the i, inhibitor ivabradine Trial (SHIFT), which is currently investigating the effects of Procoralan in congestive heart failure. The objective is to evaluate if the addition of Procoralan to standard therapy results in a further reduction of cardiovascular events in heart failure patients.

These ongoing trials should provide important evidence and insights that will enhance the care and management of patients with CAD or heart failure.

References
La maladie coronaire (MC) reste la cause principale de décès et d’invalidité dans le monde entier, malgré de nombreuses avancées thérapeutiques en cardiologie. La réduction d’une fréquence cardiaque de repos élevée est une démarche bien établie pour diminuer l’angor et l’ischémie ; elle est également recommandée comme approche thérapeutique dans la prise en charge des maladies cardio-vasculaires. Il est maintenant prouvé qu’une fréquence cardiaque élevée est un facteur de risque d’événements indésirables dans la population générale. Les résultats de l’étude BEAUTIFUL (morBidity-mortality EvaluaTion of If inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction) ont démontré qu’une fréquence cardiaque élevée (≥70 battements par minute ; bpm) augmente le risque cardio-vasculaire. Procoralan est le seul produit autorisé en pratique clinique agissant uniquement sur l’activité pacemaker cardiaque, basé sur une inhibition sélective et spécifique du courant If. La tolérance et l’efficacité cliniques de Procoralan ont été démontrées par rapport à un placebo et à des produits antiangreux déjà existants comme les β-bloquants et les antagonistes calciques. L’étude récente ASSOCIATE (evaluation of the Antianginal efficacy and safety of the asSociation Of the If Current inhibitor IvabrAdine with a beta-blockEr) a démontré que Procoralan abaissait la fréquence cardiaque de façon significative et améliorait tous les paramètres d’aptitude à l’effort chez les patients atteints d’angor stable prenant de l’aténolol (β-bloquant). Les résultats de BEAUTIFUL suggèrent que Procoralan a un rôle non seulement comme traitement symptomatique mais aussi en prévention des événements coronaires chez les patients coronaïens ayant une fréquence cardiaque ≥ 70 bpm, en plus du traitement préventif de routine. D’autres études en cours devraient permettre de prouver et de comprendre l’importance de la prise en charge des patients atteints de MC stable ou d’insuffisance cardiaque.
Despite all the therapeutic advances in the prevention and treatment of coronary artery disease (CAD), the disease remains the leading cause of death and disability worldwide. Epidemiological studies have demonstrated that an elevated heart rate is an independent predictor of cardiovascular events in CAD patients. The results of the morbidity–mortality Evaluation of the If inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction (BEAUTIFUL) have shown that patients with elevated heart rate (>70 bpm) are clearly at high risk for all cardiovascular events. Thus reducing the elevated heart rate in CAD patients could be an additional approach to lowering their risk of cardiovascular events. Ivabradine is the first of a new class of heart rate–lowering agents that act specifically on the sinoatrial node, and it has been well documented to provide antianginal and anti-ischemic efficacy in stable CAD patients. Furthermore, in stable CAD patients with associated left ventricular dysfunction and a baseline heart rate of 70 bpm or above, the use of ivabradine on top of the guideline-recommended optimal preventive therapy leads to a significant reduction in cardiovascular events. Because of these promising results with ivabradine, and given the association between heart rate and cardiovascular events in all CAD patients, the evaluation of ivabradine in acute coronary syndromes and in stable coronary patients with preserved left ventricular ejection fraction is clearly warranted. Two specific clinical studies have been designed for this purpose.

What further clinical perspectives are there for pure heart rate reduction with ivabradine in the management of CAD?

Heart rate reduction is a well accepted approach to relieving ischemia and angina in stable coronary artery disease (CAD) patients. Large scale epidemiological studies have also shown a positive association between elevated baseline heart rate and the increased risk of cardiovascular events in stable CAD patients.1

The results of BEAUTIFUL (morBidity–mortality Evaluation of the If inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction) have shown prospectively that in CAD patients with associated left ventricular dysfunction (LVD), those with a baseline heart rate of 70 beats per minute (bpm) or above have a significantly higher risk of cardiovascular morbidity and mortality.2

**Interview with K. Fox, United Kingdom**

Considering the emerging role of HR reduction as a therapeutic approach in CAD management, and the background of the important benefits of pure HR reduction with ivabradine in stable CAD patients, it was felt necessary to evaluate the effect of ivabradine in ACS (VIVIFY) as well as in CAD patients with preserved LV function (SIGNIFY). …The results of SIGNIFY could reinforce the benefits observed in BEAUTIFUL and expand them to all CAD patients with a baseline heart rate ≥70 bpm and preserved LV function.”
Ivabradine is the first of a new class of heart rate–lowering agents that act specifically on the sinoatrial node, and the drug has been well documented to provide antianginal and anti-ischemic efficacy in monotherapy and in combination with β-blockers in stable CAD patients. Furthermore, in stable CAD patients with associated LVD and a baseline heart rate of 70 bpm or above, the use of ivabradine on top of the guideline-recommended optimal preventive therapy led to a significant reduction in coronary events (Figure).

Considering the emerging role of heart rate reduction as a therapeutic approach in CAD management, and the background of the important benefits of pure heart rate reduction with ivabradine in stable coronary syndromes, as well as in CAD patients with documented preserved left ventricular ejection fraction, Evaluation of the IntraVenous I_f inhibitor ivabradine after ST-segment–elevation myocardial infarction (VIVIFY) is an ongoing trial evaluating the efficacy and safety of ivabradine in patients with acute ST-segment–elevation myocardial infarction (STEMI) undergoing percutaneous coronary intervention. To evaluate the efficacy of heart rate reduction with ivabradine in the reduction of cardiovascular outcomes in stable coronary patients with preserved ejection fraction, we have designed another morbidity–mortality study—SIGNIFY (Study assessing the morbidity–mortality benefits of the I_f inhibitor ivabradine in patients with coronary artery disease).

What is the rationale for ivabradine treatment in patients with acute coronary syndromes? When do you expect the results of VIVIFY?

Elevated heart rate is frequently observed in patients with acute myocardial infarction, and this can further aggravate the myocardial ischemia by increasing the oxygen demand and further lowering the myocardial oxygen perfusion. There is good evidence to suggest that the beneficial effects of β-blockers after acute myocardial infarction are primarily due to heart rate reduction.7 The use of early β-blocker therapy in patients with acute myocardial infarction has been shown to reduce the risk of reinfarction and ventricular fibrillation, but to increase the risk of cardiogenic shock, especially during the first day after admission.9 The use of ivabradine in these patients could be advantageous, as ivabradine reduces the heart rate without any negative inotropic effect,10 and ivabradine can also be used in patients in whom β-blockers are contraindicated or not well tolerated.11 Hence, VIVIFY was designed to evaluate the efficacy and safety of ivabradine in patients with acute STEMI who undergo a percutaneous coronary intervention. VIVIFY is a placebo-controlled randomized international trial. The first patient was recruited in May 2006 and the results are expected to be available by the end of 2009.

What could the impact be of the expected results of VIVIFY on the management of acute coronary patients?

Slowing the heart rate has always been considered as a useful approach in acute coronary patients. The results of VIVIFY have the potential to reinforce this approach and to demonstrate the safety and potential benefits of ivabradine for the first time in an acute coronary setting.

What is the rationale and objective of SIGNIFY?

Resting heart rate has been shown to be a strong predictor of overall and cardiovascular mortality in a wide range of patients, including patients with CAD and post-myocardial infarction.12 The results of BEAUTIFUL have shown that in stable CAD patients with associated LVD, heart rate reduction with ivabradine leads to a significant reduction in all coronary events in the group of patients with a baseline heart rate of 70 bpm or more. Considering the positive results

---

**SELECTED ABBREVIATIONS AND ACRONYMOS**

- **BEAUTIFUL**: morBidity-mortality EvAluaTion of the I_f inhibitor ivabra-dine in patients with coronary disease and left venticULar dysfunction
- **bpm**: beats per minute
- **CAD**: coronary artery disease
- **LVD**: left ventricular dysfunction
- **SIGNIFY**: Study assessing the morbidity–mortality benefits of the I_f inhibitor ivabradine in patients with coronary artery disease
- **STEMI**: ST-segment–elevation myocardial infarction
- **VIVIFY**: evAluation of the IntraVenous I_f inhibitor ivabradine after ST-segment–elevation myocardial infarction
with ivabradine on the coronary end points and the neutral results on the heart failure end points in CAD patients with LVD, one can postulate that ivabradine could be more beneficial in reducing cardiovascular events in CAD patients with preserved ejection fraction and a baseline heart rate of more than 70 bpm. Recent studies have also demonstrated the promising anti-atherosclerotic properties of ivabradine, once again highlighting the prominent role of ivabradine in the prevention of cardiovascular events in CAD patients. With this background in mind, we designed SIGNIFY to assess the efficacy of ivabradine compared with placebo in the prevention of cardiovascular events in patients with stable CAD without clinical heart failure, on top of guideline-recommended optimal preventive therapy. The primary end point of the study is a composite of cardiovascular death and nonfatal acute myocardial infarction.

**Which patients will be included in SIGNIFY and how long will the follow-up be?**

The inclusion and exclusion criteria of SIGNIFY have been designed to identify a group of patients who have documented stable CAD without clinical signs of heart failure and who are in normal sinus rhythm with a baseline heart rate of 70 bpm or more. The documentation of CAD will be based on previous documented myocardial infarction or previous revascularization (percutaneous intervention or coronary artery bypass graft) in two or more major coronary arteries, at least 3 months ago, or the imaging evidence of at least 50% narrowing of at least one or more major coronary arteries and a positive noninvasive stress test (exercise tolerance test, perfusion scintigraphy, or stress echocardiogram/hospitalization with documented clinical diagnosis of unstable angina within 12 months prior to selection). The left ventricular function of all patients will be assessed, and only patients with a left ventricular ejection fraction >40% will be enrolled. In addition, the presence of cardiovascular risk factor(s) will be required at inclusion: either at least one of the following—Canadian Cardiovascular Society class II (or higher) symptomatic angina, objective evidence of myocardial ischemia induced by stress testing, documented diagnosis of major coronary event (acute myocardial infarction/unstable angina) within 12 months prior to selection; or at least two of the following—documented low HDL cholesterol and/or documented high LDL cholesterol, type 1 or 2 diabetes treated with an oral hypoglycemic or insulin, documented peripheral artery disease, current smoker, age >70 years. All patients would be expected to follow a stable conventional treatment regimen that is considered optimal by the treating physician.

Apart from the usual exclusion criteria as in any clinical trial, the main exclusion criteria in SIGNIFY are related to the stability and severity of the CAD. Patients will not be included if they have had a myocardial infarction or coronary revascularization within 3 months of randomization; if they have a history of stroke or cerebral transient ischemic attack within the previous 3 months; if they have severe liver or renal disease; or if they are planning to have a revascularization procedure. Patients with clinical signs of heart failure will be excluded.

Patients meeting the inclusion criteria will be randomized to ivabradine 7.5 mg twice daily (with the possibility of up titration to 10 mg twice daily or down titration to 5 mg twice daily depending on the resting heart rate and the presence or absence of symptomatic bradycardia) or matching placebo on top of optimal preventive therapy and will be followed up for a maximum period of 42 months. We plan to follow up all patients for a minimum period of 18 months.

**When do you expect the results of SIGNIFY?**

The recruitment for SIGNIFY is expected to begin in October 2009. To obtain the necessary statistical power we need to recruit around 12 000 patients. Assuming that the recruitment goes as per our expectations, the study should be completed by 2013.

**How will SIGNIFY advance the management of patients with stable CAD?**

If the results, as expected, show that ivabradine treatment reduces morbidity and mortality in patients with resting heart rates above 70 bpm despite conventional therapy, this trial will constitute a breakthrough in treatment strategies for all stable CAD patients.

It must be acknowledged that huge strides have already been made in the prevention and treatment of CAD patients. Today, CAD patients are treated with a range of therapies that include β-blockers. Unfortunately, despite the effectiveness of these treatments, there are a large number of patients whose resting heart rate remains above 70 bpm and these patients are at a higher risk in terms of morbidity and mortality.

Specific heart rate–reducing effects may provide the advance in therapeutic strategies that is needed. With the results of BEAUTIFUL, it is already known that ivabradine reduces coronary events in stable CAD patients with associated LVD and heart rate ≥70 bpm. The results of SIGNIFY could reinforce the benefits observed in BEAUTIFUL and expand them to all CAD patients with preserved left ventricular function and a baseline heart rate of 70 bpm or more. These results could confirm that all stable CAD patients with preserved left ventricular function and a baseline heart rate ≥70 bpm could receive ivabradine as an essential part of their treatment plan in addition to their routine therapy.
La maladie coronaire (MC) demeure la cause principale de décès et d'incapacité dans le monde entier malgré toutes les avancées thérapeutiques et la prévention dont elle a bénéficié. Des études épidémiologiques ont montré qu’une fréquence cardiaque élevée est un facteur prédictif indépendant d’événements cardiovasculaires chez des patients coronariens. L’étude BEAUTIFUL (morBidity-mortality EvAlUaTion of the I inhibitor ivabradine in patients with coronary disease and left ventricular systolic dysfunction) a montré que les patients dont la fréquence cardiaque est élevée (≥ 70 bpm) sont clairement à haut risque pour tous les événements cardiovasculaires. Diminuer la fréquence cardiaque élevée des patients coronariens pourrait donc être une approche supplémentaire de la réduction de leur risque d’événements cardiovasculaires. L’ivabradine est le premier d’une nouvelle classe d’agents diminuant la fréquence cardiaque, qui agissent spécifiquement sur le nœud sino-auriculaire ; son efficacité anti-angorée et anti-ischémique chez les patients coronariens stables a été bien documentée. En outre, l’utilisation de l’ivabradine en plus des traitements préventifs recommandés par les directives chez les patients coronariens stables ayant une dysfonction ventriculaire gauche et une fréquence cardiaque initiale ≥ 70 bpm, permet une diminution significative des événements coronaires. Ces résultats prometteurs de l’ivabradine ainsi que l’association entre fréquence cardiaque et événements cardiovasculaires chez tous les patients coronariens, justifient clairement son évaluation dans les syndromes coronaires aigus et chez les patients coronariens stables à fraction d’éjection ventriculaire gauche préservée. C’est dans ce but que deux études cliniques spécifiques ont été élaborées.

Keywords: coronary artery disease; left ventricular dysfunction; heart rate; myocardial infarction; ivabradine
Resting heart rate is an easily measurable cardiovascular parameter. However, it is subject to high variability, and this may have led to an underestimation of its impact on cardiovascular morbidity and mortality. Sources of variability include physical factors, psychic stimuli, environmental factors, body position, and methods of measurement. To minimize the effects of these confounding factors, the measurement of this clinical variable should be strictly standardized.

Recommendations on how to measure resting heart rate

By P. Palatini, Italy

Resting heart rate is an easily measurable cardiovascular parameter, but is subject to high variability. Studies focusing on heart rate should take into account all possible sources of variability, including the resting period before measurement, environmental conditions, method of measurement (pulse palpation versus electrocardiogram), number of readings, duration of measurement, position of the body, and nature of the observer. To minimize the effects of these confounding factors, the measurement of this clinical variable should be strictly standardized. Exercise, alcohol, nicotine, and coffee should be avoided in the hours preceding measurement. Readings should preferably be taken by pulse palpation while the patient is comfortably seated in a chair with legs uncrossed. The room should be at a comfortable temperature and background noises should be avoided. The patient should refrain from talking during the procedure, and at least 5 minutes should elapse before the first reading is taken. Little is known about the predictive value of out-of-office heart rate measurement. Available data indicate that heart rate recorded with ambulatory monitoring or self-measured at home provides little or no additional prognostic information to heart rate measured in the clinic. However, heart rate recorded by self measurement does not involve any additional cost, thus for hypertensive subjects who undergo self blood pressure measurement, reporting of heart rate together with blood pressure data may provide useful information.

High heart rate has been shown to be an independent risk factor for all-cause and cardiovascular death in general population studies. Elevated heart rate has also been shown to provide important prognostic information in subjects with hypertension, diabetes, and coronary artery disease. Resting heart rate is an easily measurable cardiovascular parameter. However, it is subject to high variability, and this may have led to an underestimation of its impact on cardiovascular morbidity and mortality. Sources of variability include physical factors, psychic stimuli, environmental factors, body position, and methods of measurement. To minimize the effects of these confounding factors, the measurement of this clinical variable should be strictly standardized. In most published studies, information is missing on how heart rate was measured, even when heart rate was one of the major variables to measure. This prevents the reader from fully understanding the methodology of heart rate determination and from being able to compare the results coming from different laboratories. Studies focusing on heart rate should take
into account all possible causes of variability, and in particular, the resting period before measurement, the position of the body, the environmental conditions, the method of heart rate recording, and the statistical approach to data analysis.\textsuperscript{2,6}

The aim of this article is to focus upon the most important methodological problems in the assessment of heart rate, and to provide recommendations for a standardized method of measurement.

**Office and out-of-office measurement**

Most information on the prognostic significance of heart rate has been obtained from studies that used heart rate measured under resting conditions. However, as mentioned above, resting heart rate is subject to high variability, and may be influenced by the nature of the observer. In fact, Mancia et al showed that the actual visit to a doctor caused a heart rate increase of as high as 45 beats per minute (bpm), with a mean increase of 16 bpm.\textsuperscript{7} This suggests that heart rate measured out of the office, either with ambulatory measurement or self assessment, might be more representative of a subject’s usual heart rate. A study in 839 hypertensive subjects showed that the reproducibility of heart rate recorded twice 3 months apart was better for ambulatory than office measurement.\textsuperscript{8} Reproducibility of office heart rate was particularly poor when it was above the level of 85 bpm. The above data indicate that heart rate recorded with ambulatory monitoring has better reproducibility than office heart rate, and could, thus, have a stronger association with outcome than resting heart rate measured in the office. However, only a few studies have examined the association between ambulatory heart rate and total or cardiovascular mortality. Recent results from the Ohasama study showed that neither daytime nor nighttime heart rate predicted cardiovascular disease mortality, whereas both could predict noncardiovascular disease mortality.\textsuperscript{9} The lack of association between heart rate and cardiovascular death found in the Ohasama cohort might be due in part to a dilution effect caused by the preponderance of female participants within this cohort (>64%).

In a recent analysis of six study populations, 24-hour heart rate predicted total and noncardiovascular mortality, but not cardiovascular mortality or any of the combined fatal and nonfatal events.\textsuperscript{10} The above data are in agreement with previous results obtained in the Syst-Eur cohort,\textsuperscript{11} and indicate that heart rate measured with ambulatory recording is of little use for stratifying cardiovascular risk. Even less is known on the predictive value of self heart rate measurement. Data from the Ohasama study showed a 17% increase in the risk of mortality for a 5-bpm increase in home heart rate,\textsuperscript{12} whereas as in the PAMELA study (Pressioni Arteriose Monitorate E Loro Associazioni), no association was found between home heart rate and mortality.\textsuperscript{13} However, heart rate recorded with self blood pressure measurement does not imply any additional cost, and thus it is the opinion of the experts that the reporting of heart rate together with blood pressure data in hypertensive patients who undergo self blood pressure measurement may provide useful information.\textsuperscript{2}

\begin{table}[h]

<table>
<thead>
<tr>
<th>Method of measurement</th>
<th>Heart rate at rest</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Measurement of heart rate at rest</strong></td>
<td><strong>Duration of measurement</strong></td>
</tr>
<tr>
<td>To achieve a stable hemodynamic condition, the patient should rest for at least 5 minutes, although in subjects with a pronounced white-coat reaction, a longer period may be necessary. The duration of measurement ranges from 15 seconds to 1 minute in different studies.\textsuperscript{2,6} According to the aforementioned European consensus panel,\textsuperscript{6} 30 seconds seem to be sufficient to obtain a reliable estimate of heart rate, because in most patients, 30 to 40 cardiac cycles can be averaged out. In subjects with a very low heart rate, a longer period may be necessary.</td>
<td></td>
</tr>
<tr>
<td><strong>Office and out-of-office measurement</strong></td>
<td><strong>Methods of measurement</strong></td>
</tr>
<tr>
<td>The patient should be allowed to sit for at least 5 minutes in a quiet room at a comfortable temperature.</td>
<td>The patient should be allowed to sit for at least 5 minutes in a quiet room at a comfortable temperature.</td>
</tr>
<tr>
<td>Heart rate should be measured over a 30-second period by pulse palpation.</td>
<td>Heart rate should be measured over a 30-second period by pulse palpation.</td>
</tr>
<tr>
<td>At least two measurements in the sitting position should be taken.</td>
<td>At least two measurements in the sitting position should be taken.</td>
</tr>
<tr>
<td>In subjects in whom orthostatic blood pressure measurement is performed, heart rate should be measured after each blood pressure reading.</td>
<td>In subjects in whom orthostatic blood pressure measurement is performed, heart rate should be measured after each blood pressure reading.</td>
</tr>
<tr>
<td>Result may vary according to whether heart rate is measured by a doctor, a nurse, or an automatic device.</td>
<td>Result may vary according to whether heart rate is measured by a doctor, a nurse, or an automatic device.</td>
</tr>
<tr>
<td>Patients performing self blood pressure measurement should also collect heart rate data.</td>
<td>Patients performing self blood pressure measurement should also collect heart rate data.</td>
</tr>
</tbody>
</table>

**Table.** Procedures for heart rate measurement.


**Selected abbreviations and acronyms**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>BEAUTIFUL</td>
<td>morBidity-mortality EvaLuAtion of the I, inhibitor (\text{ib} ) and left ventricular dysfunction</td>
</tr>
<tr>
<td>CASTEL</td>
<td>Cardiovascular Study in the Elderly</td>
</tr>
<tr>
<td>HARVEST</td>
<td>Hypertension and Ambulatory Recording Venetia Study</td>
</tr>
<tr>
<td>PAMELA</td>
<td>Pressioni Arteriose Monitorate E Loro Associazioni (study)</td>
</tr>
</tbody>
</table>

**Recommendations on how to measure resting heart rate – Palatini**

MEDICOGRAPHIA, Vol 31, No 4, 2009 415
**Focus**

◆ **Number of measurements**

It is known that heart rate tends to fall when measured repeatedly; this is because patients need time to adjust to the doctor’s office setting. This decrease is rather small, however, as shown by the results of the Hypertension and Ambulatory Recording Venetia Study (HARVEST) and the Cardiovascular Study in the Elderly (CASTEL).14,15 In HARVEST, for instance, heart rate decreased by approximately 2 bpm over a period of 2 months.14 However, temporal changes in heart rate remarkably varied among individuals. It would seem desirable, therefore, to obtain an adequate number of measurements before making a diagnosis—especially in patients whose heart rate shows a substantial decline from the first to the second reading. However, in CASTEL, single baseline measurements all had great predictive value for cardiovascular mortality, and the mean of three measurements increased the predictive power only marginally.15 Thus, two measurements seem to be sufficient for a reliable estimate of resting heart rate in most patients. It should be kept in mind that the extent to which heart rate increases during the alarm reaction to the measurement largely depends on the nature of the observer, being higher if heart rate is measured by a doctor, intermediate if it is measured by a nurse, and lower if it is acquired with an automatic device in the absence of an observer.2,16 Thus, when comparing data from different laboratories, it is of paramount importance to know the nature of the observer.

◆ **Body position**

The choice of body position during heart rate measurement is also a source of controversy in the literature, where roughly half of epidemiological studies report using sitting heart rate, and the other half supine heart rate.12 However, in clinical studies, the supine position has been more frequently employed (Figure). There are no objective data to suggest that one position is better than the other. In the supine position, one should expect a heart rate that is 1-2 bpm higher than in the lying position. In experimental studies requiring a long period of rest in order to achieve a stable hemodynamic condition, the supine position should be preferred. However, the sitting position is preferable for epidemiological studies or clinical routine assessment in which heart rate can be measured at the end of each blood pressure measurement. Heart rate may also provide useful clinical information when measured in the standing position, especially in elderly hypertensive patients who frequently have a drop in blood pressure while standing up, and in young hypertensive individuals who may be hyper-reactive to standing.17

◆ **Measurement of heart rate during exercise**

As many studies have consistently documented that measurement of heart rate during exercise and recovery is useful for identifying subjects at increased cardiovascular risk, careful monitoring of heart rate is mandatory whenever a subject undergoes exercise testing.18-20 In asymptomatic men and women, as well as in symptomatic referral populations, an inability of the heart to increase its rate appropriately during incremental exercise has been shown to be of prognostic value independent of traditional risk factors, other markers of risk derived from exercise testing, or thallium ischemia, and to also be independently predictive of death in patients with cardiac diseases.18,19 The chronotropic measurements most commonly used in the literature include absolute heart rate during submaximal exercise, absolute peak of heart rate achieved, change in heart rate from rest to peak exercise, one standard deviation of mean peak heart rate achieved, 80% to 85% age-predicted target heart rate, and the so-called “chronotropic index,” which takes into account age, physical fitness, resting heart rate, and the age-predicted maximum heart rate.21 According to a recent report by Savonen and colleagues,12 the slope of the increase in heart rate during exercise on a bicycle ergometer (maximal heart rate minus heart rate at 40% workload) has greater prognostic power than other exercise-derived chronotropic measurements. The 100%-40% heart rate slope depends chiefly on the response of the sympathetic nervous system, and does not include the early portion of the slope, which mainly reflects the withdraw-
al of the vagal tone, suggesting that the main factor mediating the association between chronotropic incompetence and mortality is a reduced ability to increase sympathetic activity. It has not been well established as to whether the prognostic information provided by heart rate assessment during exercise can provide complementary information to that provided by heart rate measured under resting conditions. However, whenever exercise is performed for diagnostic purposes with either a bicycle or a treadmill ergometer, measurement of heart rate throughout the exercise and recovery period is highly recommended.

Techniques for heart rate measurement

It is not known whether it is better to measure heart rate with an electrocardiogram or rather to take the pulse rate. The electrocardiogram would appear to be more accurate, but the number of cardiac cycles used for heart rate calculation is usually quite small. As mentioned, in most studies providing heart rate data, information on the method of measurement is missing.22 Whereas in epidemiological studies roughly 50% of the measurements are obtained by pulse palpation and 50% by electrocardiographic recording,21 in the majority of clinical studies, the latter technique has been used (Figure). Recently, electronic pulse meters were made available for measuring heart rate automatically from the finger, wrist, or chest.22 These devices allow measurements to be taken continuously, and can be used during exercise when manual measurement would be difficult or impossible.

◆ Pulse palpation

Traditionally, heart rate has been measured by pulse palpation. The pulse rate is measured by counting the beats in a set period of time (from 15 to 60 seconds) and multiplying that number to get the number of bpm. This is still the method currently used by doctors and other healthcare professionals in daily routine. The pulse rate can be measured at any point on the body where an artery is close to the surface. Most common places are radial, carotid, brachial, and femoral arteries. If stroke volume is subject to high variability such as in cases of atrial fibrillation, some heart beats can be missed at pulse palpation, and heart rate should be measured directly from heart auscultation.

◆ Electrocardiography

There are, however, techniques that allow heart rate to be measured more precisely and for longer periods of time. Electrocardiographic recording is the most precise method of heart rate measurement and is routinely carried out in many clinical settings, especially in critical care medicine. Whether electrocardiographic measurement may also be advantageous in epidemiological studies or in clinical routine is not known, however. The use of electrocardiography obviously implies greater financial costs, and it is not known whether increased measurement precision actually translates into more meaningful data. According to Erikssen et al, the two measurements are highly correlated (R>0.9) and provide similar information.23 For this reason, electrocardiographic measurement is not recommended for the measurement of resting heart rate, even in research.

◆ Electronic devices

Electronic pulse meters consist of two parts, a transmitter placed over the artery and a receiver attached to a belt worn around the chest or a wrist watch receiver for display. A photo diode or a photo transistor can be used to detect pulse rate. The skin may be illuminated with visible (red) or infrared light emitting diodes using transmitted or reflected light for detection. Infrared sensors can easily be clipped to finger ends or ear lobes to detect the heart beat using plethysmographic technology.22 Because of frequent noise sources that may produce disturbance signals, valid pulse measurement requires extensive preprocessing of the raw signal. New systems combine analog and digital signal processing to suppress disturbance signals. A digital system is usually accurate to within 3-4 bpm. Simple heart rate monitors may only display the heart rate on the screen. More professional monitors are available that can be set to record time, calculate average and maximum heart rate for a given period, and sound an alarm when a person reaches or exceeds a predetermined target heart-rate zone. These devices are used mostly by athletes and sportspeople wishing to monitor their workouts in order to achieve their desired training benefit. More complex ambulatory devices can also record other biological signals such as breathing movements, nasal and oral flow, and blood oxygen saturation, which can be useful for monitoring sleep apnea episodes.24

Recommendations before measurement

These recommendations are roughly the same as those used for blood pressure measurement. As mentioned, several physical or psychological factors can influence the assessment of heart rate during the office visit.1-3 In particular, exercise, alcohol, nicotine, and coffee can influence the heart rate and should be avoided in the hours preceding measurement. Readings should preferably be taken while the patient is seated in a chair. The patient should be comfortably seated, with legs uncrossed, and examined in a room with a comfortable temperature, avoiding any background noise such as telephones or beepers. The patient should refrain from talking during the procedure, and at least 5 minutes should elapse before the first reading is taken. Although heart rate should be measured in any subject under medical investigation, this hemodynamic variable is usually assessed in patients with hypertension or cardiac disease. Most of these patients are receiving pharmacological therapy, and the doctor should be aware that many cardiovascular drugs can either decrease or increase the heart rate.

The bradycardic effect is particularly pronounced for two classes of drugs, β-blockers and inhibitors of the so-called
“funny” current in the sinus node pacemaker cells. The best known agent in this class, ivabradine, produces a dose-dependent reduction in heart rate both at rest and during exercise, which is of the same magnitude as that seen with β-blockers. Nondihydropyridine calcium antagonists such as the phenylalkylamines and benzothiazepines also have a bradycardic action, although this is smaller than that seen with β-blockers or β current inhibitors. The centrally acting antihypertensive drugs guanfacine, clonidine, and methyl-dopa have a bradycardic effect of similar magnitude to that of the nondihydropyridine calcium antagonists. By contrast, the central 1-imidazoline receptor agonists moxonidine and rilmenidine have a negligible effect on heart rate. A slight bradycardic action has been described for the angiotensin II type 1 receptor blocking agents, but this might be due to an adaptation process that takes place during the observation period rather than to a true bradycardic effect.

Some classes of antihypertensive agents can trigger a reflex increase in heart rate due to the sympathetic activation that occurs in response to the fall in blood pressure. Vasodilators such as minoxidil or hydralazine can produce remarkable increases in heart rate. The effect of nitrates on the arteriolar circulation is smaller, and a tachycardic effect of these drugs is less frequently observed. An increase in heart rate chiefly during acute administration has also been observed with α-blockers such as prazosin or doxazosin, or with urapidil, a drug combining peripheral α-adrenergic blockade with a central effect. However, the heart rate increase is somewhat less pronounced with urapidil than with pure α-blockers. An increase in heart rate can also be seen with the short-acting dihydropyridine calcium antagonists, but rarely with the long-acting ones.

Who should be considered at risk?
Under resting conditions, the adult human heart beats at about 70 to 75 bpm, and the heart rate tends to decrease with age. Women generally have a 3- to 7-bpm higher heart rate than men. The normal limits of resting heart rate are nominally between 60 and 100 bpm. However, the results of most epidemiologic studies indicate that this normality interval cannot be applied to heart rate when considering it as a cardiovascular risk factor. In fact in many studies, heart rates higher than 80-85 bpm have been shown to imply a considerable increase in risk. Conversely, heart rates lower than 60 bpm have been shown to confer a protective effect against cardiovascular disease. It is therefore evident that the 60- to 100-bpm range can no longer be considered as the normal interval for resting heart rate. Most epidemiological studies have shown that there is a considerable increase in risk with heart rates higher than 80-85 bpm, and thus the upper normal limit for this clinical variable could be—albeit arbitrarily—set at this level.

Similar results have been obtained by our group using an objective method for identifying the partition level between normal and high heart rates. Using mixture analysis in several general or hypertensive populations, we found that the cut-off between people with a normal heart rate and those with a high heart rate was between 80 and 85 bpm. According to some authors, the upper limit of normal of a clinical variable should be defined as the level at which the benefits of therapeutic intervention exceed potential risks. β-Blockers have been found to be beneficial among patients with heart failure or myocardial infarction only if heart rate is higher than 80-85 bpm. Based on this approach, the upper limit of normal should be set—at least in heart failure and post–myocardial infarction patients—at a heart rate of 80-85 bpm with a therapeutic target of 60 bpm or lower. The recent study BEAUTIFUL (mor-Bidity-mortality EvAlUaTion of the β inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction) added substantially to current knowledge concerning the threshold at which risk increases in coronary patients taking β-blockers. Patients in the placebo group (most of whom took β-blockers) with a baseline resting heart rate of 70 bpm or more had an increased risk for all cardiovascular outcomes after adjustment for other predictors of outcome. These data indicate that special attention should be given to this high risk group with a resting heart rate above 70 bpm, who are at a high risk of cardiovascular events.

References
10. Hansen TW, Thiis L, Boggia J, et al. Prognostic value of ambulatory heart rate re-
RECOMMANDATIONS SUR LA MESURE DE LA FRÉQUENCE CARDIAQUE AU REPOS

La fréquence cardiaque au repos est un paramètre cardiovasculaire facilement mesurable mais susceptible de grandes variations dont les études qui s’y consacrent devraient tenir compte : période de repos avant la mesure, environnement, méthode de mesure (palpation du pouls versus électrocardiogramme), nombre de relevés, durée de la mesure, position du corps et nature de l’observateur en sont autant d’exemples. La mesure de la fréquence cardiaque doit être strictement standardisée pour diminuer l’effet de ces facteurs de confusion : pas d’effort, ni d’alcool, ni de nicotine ou café dans les heures précédant la mesure, préférer la mesure par prise de pouls sur un patient que l’on aura laissé pendant au moins 5 minutes confortablement assis sur une chaise, jambes décroisées, dans un environnement, méthode de mesure (palpation du pouls versus électrocardiogramme), nombre de relevés, durée de la mesure, position du corps et nature de l’observateur en sont autant d’exemples. La mesure de la fréquence cardiaque doit être strictement standardisée pour diminuer l’effet de ces facteurs de confusion : pas d’effort, ni d’alcool, ni de nicotine ou café dans les heures précédant la mesure, préférer la mesure par prise de pouls sur un patient que l’on aura laissé pendant au moins 5 minutes confortablement assis sur une chaise, jambes décroisées, dans une pièce silencieuse à température confortable et qui évitera de parler pendant la prise. La valeur prédictive de la mesure de la fréquence cardiaque en dehors du cabinet médical est peu connue. Il semblerait que la fréquence cardiaque mesurée en ambulatoire par enregistrement ou automeasure à domicile ne fournisse que peu voix pas d’informations pronoctiques supplémentaires à la fréquence cardiaque mesurée en consultation. Cette automeasure n’engendrant néanmoins aucun coût, elle pourrait être utile concomitamment à l’automesure de la pression artérielle chez des patients hypertendus.

Keywords: heart rate; measurement; assessment; exercise; resting; ambulatory
Prevention of endothelial dysfunction with pure heart rate reduction

By J. Yang and J.-C. Tardif, Canada

Endothelial dysfunction plays a major role in the cardiovascular disease continuum, facilitating inflammation, platelet aggregation, and coronary vasoconstriction. Experimental and clinical data clearly suggest that endothelial dysfunction has pro-atherosclerotic and prothrombotic effects and has important predictive value for future cardiovascular events in patients with coronary artery disease. New data demonstrating the effect of increased heart rate on the development of endothelial dysfunction may provide a new understanding about the basis for the association between increased heart rate and cardiovascular outcomes. The protective effect on the endothelium from long-term pure heart rate reduction with ivabradine that we have shown in a dyslipidemic mouse model of endothelial dysfunction could provide an important mechanism for the potential cardioprotective benefits of ivabradine. These data also demonstrate that the β-blocker metoprolol did not provide the same protection despite the same magnitude of heart rate reduction.

Despite the advances made in the development of efficacious treatments for coronary heart disease (CHD), it remains the first cause of mortality in Western populations. This has led to additional research efforts directed at improving our understanding of the underlying mechanisms responsible for the development of adverse cardiovascular events, in an attempt to find alternative and superior means of treatment. Some of the widely accepted risk factors for CHD that have become targets for therapies include high blood pressure, dyslipidemia, smoking, diabetes, obesity, and physical inactivity. An inverse semi-logarithmic relationship has been observed between longevity and resting heart rate in mammals (Figure 1), although human beings seem to be the exception to this rule, potentially because of the medical advances that prolong human life expectancy. Observation of this relationship has led to the concept that a fixed number of heartbeats is allocated, after which we inevitably expire. An elevated resting heart rate has also been shown in epidemiological studies to be independently associated with mortality from cardiovascular as well as noncardiovascular diseases.

Heart rate: sinoatrial node and I_f current
Heart rate in humans is set by the sinoatrial (SA) node. The SA node cells spontaneously depolarize during diastole and initiate the next action potential. It is this characteristic that confers on them their inherent pacemaker ability. The SA node has many intrinsic qualities. Specifically, it has a seemingly fail-safe nature; many
currents are responsible for the spontaneous depolarization of the SA node, and the selective blocking of one of these currents does not put one’s life at risk.\textsuperscript{5} This fact was demonstrated clinically using a drug that specifically and completely inhibits the \( I_f \) current (also referred to as the “funny” current), which is one of the main currents responsible for SA node depolarization. The complete blockade of the \( I_f \) current was shown to reduce the heart rate by approximately 30%.\textsuperscript{6}

Other drugs available for the treatment of CHD include calcium channel antagonists and long-acting nitrates. The former have been associated with peripheral edema, constipation, and negative inotropic effects,\textsuperscript{7,8} as well as with a higher risk of precipitating or potentiating heart failure or atrioventricular node dysfunction. The use of nitrates has been associated with headaches, lightheadedness, and syncope.\textsuperscript{9} The continuous use of long-acting nitrates can lead to pharmacological tolerance,\textsuperscript{10} but intermittent use has been associated with rebound angina.

\textbf{Ivabradine}

Ivabradine, a drug that specifically targets the \( I_f \) current, has generated interest in the medical community because of its higher specificity for decreasing heart rate than the aforementioned drugs. Several studies have been conducted in order to ascertain its safety, efficacy, and noninferiority to other drugs available clinically for the prevention of angina.

When compared with placebo in the absence of any background antianginal therapy, ivabradine has been shown to exert anti-ischemic and antianginal effects with prolonged time to 1-mm ST-segment depression during exercise testing and reduced angina frequency and nitroglycerin use.\textsuperscript{11} Ivabradine was also evaluated in several noninferiority trials during its drug development program. Ivabradine was compared with the calcium channel antagonist amlodipine\textsuperscript{12} and was shown to be noninferior to amlodipine in terms of its anti-ischemic and antianginal effects. In addition, heart rate both at rest and during exercise decreased significantly more with ivabradine than amlodipine.

Ivabradine was also compared with the \( \beta \)-adrenoceptor antagonist atenolol in the \textit{International Trial of the Antianginal effec\textsuperscript{T} of IVabradinE} compared with atenolol (\textsc{INITIATIVE}).\textsuperscript{13} Although atenolol showed greater heart rate reduction, ivabradine was noninferior (and actually even tended to be superior) and symptomatic conduction block in patients with intrinsic atrioventricular node disease.\textsuperscript{14} Furthermore, \( \beta \)-blockers have negative inotropic effects\textsuperscript{15} and can also have negative metabolic effects (on blood glucose\textsuperscript{16} and lipids\textsuperscript{17}).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{heart_rate_life_expectancy.png}
\caption{Relationship between resting heart rate and life expectancy in mammals, according to size. After reference 3: Levine HJ. J Am Coll Cardiol. 1997;30:1104-1106. Copyright \textcopyright 1997, Elsevier.}
\end{figure}

\textbf{Drugs available for the treatment of coronary heart disease}

In the past decades, \( \beta \)-blockers have been the drug class of choice for the treatment of angina. Their effect is largely attributable to their ability to lower the heart rate. Unfortunately, the use of \( \beta \)-blockers has been linked to side effects such as fatigue, lack of energy, depression, and erectile dysfunction. \( \beta \)-Blockers have also been associated with increased symptoms of peripheral arterial occlusive disease and with a potential rebound effect when ceased abruptly,\textsuperscript{18} worsened symptoms associated with obstructive pulmonary disease,\textsuperscript{19} and symptomatic conduction block in patients with intrinsic atrioventricular node disease.\textsuperscript{20} Furthermore, \( \beta \)-blockers have negative inotropic effects\textsuperscript{21} and can also have negative metabolic effects (on blood glucose\textsuperscript{22} and lipids\textsuperscript{23}). Other drugs available for the treatment of CHD include calcium channel antagonists and long-acting nitrates. The former have been associated with peripheral edema, constipation, and negative inotropic effects,\textsuperscript{24} as well as with a higher risk of precipitating or potentiating heart failure or atrioventricular node dysfunction. The use of nitrates has been associated with headaches, lightheadedness, and syncope.\textsuperscript{25} The continuous use of long-acting nitrates can lead to pharmacological tolerance,\textsuperscript{26} but intermittent use has been associated with rebound angina.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{heart_rate_life_expectancy.png}
\caption{Relationship between resting heart rate and life expectancy in mammals, according to size. After reference 3: Levine HJ. J Am Coll Cardiol. 1997;30:1104-1106. Copyright \textcopyright 1997, Elsevier.}
\end{figure}

\textbf{Drugs available for the treatment of coronary heart disease}

In the past decades, \( \beta \)-blockers have been the drug class of choice for the treatment of angina. Their effect is largely attributable to their ability to lower the heart rate. Unfortunately, the use of \( \beta \)-blockers has been linked to side effects such as fatigue, lack of energy, depression, and erectile dysfunction. \( \beta \)-Blockers have also been associated with increased symptoms of peripheral arterial occlusive disease and with a potential rebound effect when ceased abruptly,\textsuperscript{18} worsened symptoms associated with obstructive pulmonary disease,\textsuperscript{19} and symptomatic conduction block in patients with intrinsic atrioventricular node disease.\textsuperscript{20} Furthermore, \( \beta \)-blockers have negative inotropic effects\textsuperscript{21} and can also have negative metabolic effects (on blood glucose\textsuperscript{22} and lipids\textsuperscript{23}). Other drugs available for the treatment of CHD include calcium channel antagonists and long-acting nitrates. The former have been associated with peripheral edema, constipation, and negative inotropic effects,\textsuperscript{24} as well as with a higher risk of precipitating or potentiating heart failure or atrioventricular node dysfunction. The use of nitrates has been associated with headaches, lightheadedness, and syncope.\textsuperscript{25} The continuous use of long-acting nitrates can lead to pharmacological tolerance,\textsuperscript{26} but intermittent use has been associated with rebound angina.

\textbf{Ivabradine}

Ivabradine, a drug that specifically targets the \( I_f \) current, has generated interest in the medical community because of its higher specificity for decreasing heart rate than the aforementioned drugs. Several studies have been conducted in order to ascertain its safety, efficacy, and noninferiority to other drugs available clinically for the prevention of angina.

When compared with placebo in the absence of any background antianginal therapy, ivabradine has been shown to exert anti-ischemic and antianginal effects with prolonged time to 1-mm ST-segment depression during exercise testing and reduced angina frequency and nitroglycerin use.\textsuperscript{11} Ivabradine was also evaluated in several noninferiority trials during its drug development program. Ivabradine was compared with the calcium channel antagonist amlodipine,\textsuperscript{12} and was shown to be noninferior to amlodipine in terms of its anti-ischemic and antianginal effects. In addition, heart rate both at rest and during exercise decreased significantly more with ivabradine than amlodipine.

Ivabradine was also compared with the \( \beta \)-adrenoceptor antagonist atenolol in the \textit{International Trial of the Antianginal effec\textsuperscript{T} of IVabradinE} compared with atenolol (\textsc{INITIATIVE}).\textsuperscript{13} Although atenolol showed greater heart rate reduction, ivabradine was noninferior (and actually even tended to be superior)
to the β-blocker in terms of prolonging total exercise duration (primary end point) as well as time to limiting angina and angina onset during exercise tolerance testing. Thus, ivabradine induced a similar or greater improvement in exercise capacity while causing less reduction in rate-pressure-product and heart rate when compared with atenolol. According to these findings, ivabradine possessed greater efficiency in its ability to increase exercise capacity for each beat of heart rate reduction; this phenomenon can only be linked to its lack of negative inotropic, peripheral vascular, or coronary vasoconstrictor effects.20 Accordingly, this study also concluded that ivabradine was noninferior to atenolol in terms of its antianginal and anti-ischemic effects for all exercise parameters. The long-term beneficial effects of ivabradine have also been established in patients with stable angina pectoris, as it reduced the frequency of angina over the course of a 1-year study.21

More recently, the results of BEAUTIFUL (morBidity-mortality EvAllUaTion of the Iβ inhibitor ivabradine in patients with coronary disease and left ventricUlar dysfunction) have been reported.22 Although the primary end point of the study was not met in the overall population, ivabradine reduced the risks of coronary events by 22% (P=0.023) and fatal and nonfatal myocardial infarction by 36% (P=0.016), and reduced coronary revascularization by 30% (P=0.016) in the subgroup of patients with a baseline heart rate ≥70 bpm.

Ivabradine is generally well tolerated.23 The most common side-effect is phosphenes, which are visual symptoms of a transient nature related to the presence of a channel in the retina that is very similar to the hyperpolarization-activated cyclic nucleotide-gated family of ion channel subunits in the SA node.24 These visual symptoms are dose dependent, mild, and spontaneously resolve during treatment or after treatment cessation. Overall, only 1% of patients withdrew from treatment for this reason in clinical trials. Bradycardia has been reported in 2.2% of patients in clinical studies. Ivabradine does not alter the action potential and the corrected QT interval.24 In addition, ivabradine does not have a negative inotropic effect or a rebound effect when therapy is ceased abruptly, and has not been found to interfere with respiratory function.25

The missing link
Over the years, investigators have attempted to identify the missing link between slower heart rate and decreased cardiovascular events. A number of studies point to endothelial dysfunction as this missing link. The hypothesis is that higher heart rate could increase the twisting of large epicardial arteries during systole as well as the number of times per minute that forces are applied to the vascular wall, leading both to fatigue, causing endothelial damage in these vital arteries, and a simultaneous increase in the probability of atherosclerotic plaque rupture in the coronary arteries thereby leading to myocardial infarction. Endothelial dysfunction was already considered an integral part of the events leading to atherosclerosis initiation and progression, and has been shown to be associated with adverse cardiovascular events. We will now review the evidence linking heart rate and endothelial function.

**Vascular endothelium**
The endothelium serves many functions in maintaining a state of equilibrium in the cardiovascular tree. Normally, there is a balance between factors promoting and preventing thrombosis, whereby the undamaged endothelium favors anti-thrombosis. The endothelial cells normally host anti-thrombotic molecules on their surface such as heparin sulfate, thrombomodulin, and plasminogen activator, and produce and release anti-thrombotic molecules such as nitric oxide and prostacyclin in the vessel. On the other hand, once the integrity of the endothelium is compromised, for instance under situations of stress or exposure to traditional cardiovascular risk factors, the endothelium can produce prothrombotic molecules, thus tipping the balance toward prothrombosis in the vessel. Normally functioning endothelium also inhibits smooth muscle cell migration and proliferation. The endothelium is also naturally anti-inflammatory by resisting adhesion of leukocytes under normal conditions, and is impermeable to large molecules. Dysfunctional endothelium, by contrast, promotes inflammation in the vascular wall, contributing to both atherosclerosis progression and acute coronary events. Last but undoubtedly not least, the endothelium can secrete vasoconstrictor molecules, such as nitric oxide and prostacyclin, and vasoconstrictor molecules such as endothelin. Under normal circumstances, the endothelium favors vasodilation over vasoconstriction. This last characteristic promotes the patency of the vessels against progressive narrowing of the lumen in atherosclerosis.25

Endothelial dysfunction is central in the pathogenesis of atherosclerosis. It is the first step leading to the formation of fatty streaks, which is the first in a series of events that can eventually lead to the formation of atherosclerotic plaques and thrombus. Endothelial dysfunction allows lipoproteins to enter in the intima and to then be modified in situ by oxidation and glycation. These events will exacerbate endothelial dysfunction and promote macrophage adhesion to the endothelium and migration into the intima. Subsequently, the generation of extracellular matrix will promote the formation of a fibrofatty lesion, the atherosclerotic plaque. Under conditions of hemodynamic stress and degradation of extracellular matrix, the plaque can rupture and promote the formation of an intraluminal thrombus leading to an acute coronary syndrome (Figure 2).26 As mentioned, normal endothelial function is essential in maintaining the integrity of the cardiovascular system. Therefore, endothelial dysfunction is an early indicator of cardiovascular disease. Thus, one way to demonstrate the efficacy of a cardioprotective drug is to demonstrate its ability to preserve or improve endothelial function.27
Several epidemiological studies have previously demonstrated that a lower heart rate is associated with lower rates of adverse cardiovascular events and death. Other studies have suggested that a high heart rate may play a role in the formation and progression of atherosclerotic plaques. Strawn et al have demonstrated that stress-induced tachycardia is associated with atherosclerosis and dysfunction of coronary artery endothelial cells. A slower heart rate was associated in cynomolgus monkeys with less severe atherosclerotic plaques in coronary and carotid arteries. In addition, Korshunov and Berk have demonstrated the relationship between heart rate in low shear stress conditions and the degree of vascular wall remodeling. Nevertheless, none of these studies evaluated the effects of pure heart rate reduction on endothelial function.

Pure heart rate reduction with ivabradine to preserve endothelial function

We performed a study in dyslipidemic mice to document the effects of pure heart rate reduction on endothelial function. Ivabradine was chosen because it reduces heart rate in mice independently of sympathetic activation, and it does not affect blood pressure, myocardial contractility, or intracardial conduction. Endothelial vasodilator capability was used as the means to show preservation of endothelial function. The experiments were conducted in dyslipidemic mice expressing the human apoprotein-B 100, as they develop changes in endothelial-dependent arterial dilation. Dyslipidemic mice were assigned to 3 months of treatment with ivabradine, metoprolol, or no treatment.
The outcomes in terms of vessel dilation in left and right renal and posterior communicating cerebral arteries were compared between these groups and those of wild-type C57Bl/6 mice.

Acetylcholine was administered on all preconstricted arteries to measure dilator response. As free radicals impair renal endothelial function in dyslipidemic mice, the antioxidant N-acetylcysteine or the inhibitor of endothelial nitric oxide synthase (eNOS) Nω-nitro-L-arginine (L-NNA) was administered before the use of acetylcholine to better understand the mechanisms of drug effects. In cerebral arteries, dilation with acetylcholine was preceded by the inhibition of cyclo-oxygenase (COX) with indomethacin or in the presence of catalase, the latter inactivating the endothelium-derived relaxing factor hydrogen peroxide (H2O2) in these arteries.

Throughout the experiments, it was found that heart rate remained stable in wild-type mice, while it increased in untreated dyslipidemic mice. The use of ivabradine reduced heart rate in dyslipidemic mice by 17% (P<0.05). It was also shown that ivabradine prevented the appearance of left ventricular dysfunction in dyslipidemic mice, as shown by the limited increase in minimal and end-diastolic left ventricular pressure. The maximal left-ventricular systolic pressure and contractility remained unchanged in dyslipidemic mice. Ivabradine did not have any direct vascular effects on the renal and cerebral arteries.

Renal arteries
Endothelium-dependent dilation in response to acetylcholine was decreased in untreated dyslipidemic mice compared with those treated with ivabradine, which maintained maximal dilation (Figure 3). Therefore the use of ivabradine completely prevented the impaired dilator response to acetylcholine in dyslipidemic mice. The use of the antioxidant N-acetylcysteine fully restored dilation in response to acetylcholine in dyslipidemic mice, whereas it did not affect response to acetylcholine in wild-type mice and in mice treated with ivabradine (Figure 3). This shows that the endothelial dysfunction in dyslipidemic mice is caused in large part by oxidative stress, which was not increased in wild-type mice and dyslipidemic mice treated with ivabradine. Therefore, ivabradine protected the treated dyslipidemic mice against oxidative stress.

Given that ivabradine has no direct antioxidant effects, the protection it afforded might be due to alternative mechanisms such as improvement of the shear stress–dependent stimulation of the endothelium, which favors eNOS and/or prevents nitric oxide or H2O2 degradation, or decreased mechanical fatigue of the arterial wall associated with pure heart reduction.

The use of L-NNA, an eNOS inhibitor, did not exacerbate the already altered vasodilator response to acetylcholine in untreated dyslipidemic mice. It did, however, reduce vasodilation in wild-type and dyslipidemic mice treated with ivabradine.
Figure 4. Endothelium-dependent dilation of pressurized cerebral arteries (60 mm Hg) in response to acetylcholine (control), isolated from (A) 6-month-old wild-type mice (B) dyslipidemic mice (C) dyslipidemic mice treated with ivabradine (10 mg/kg/day; from age 3 to 6 months).

The effects of hydrogen peroxide inactivation by catalase (100 U/ml) and COX inhibition by indomethacin (10 mM) were tested in separate segments of cerebral arteries isolated from the same animal. Data are mean ± standard error of the mean. ‡P<0.05 compared with control.

Abbreviations: ACh, acetylcholine; CAT, catalase; INDO, indomethacin.


Figure 5. The effects of chronic treatment with ivabradine and metoprolol from the age of 3 months.

On (A) the percentage increase in heart rate measured under anesthesia in dyslipidemic mice observed at 4.5 and 6 months of age. (B) and (C) Endothelium-dependent dilator responses to acetylcholine of pressurized renal (B) and cerebral (C) arteries preconstricted with phenylephrine, isolated from 6-month-old wild-type mice, dyslipidemic mice, and dyslipidemic mice treated with metoprolol (80 mg/kg/day; from age of 3 to 6 months). Data are mean ± standard error of the mean. ‡P<0.05 compared with wild type; *P<0.05 compared with dyslipidemic mice.

Abbreviations: ACh, acetylcholine; DL, dyslipidemic; HR, heart rate; IVA, ivabradine; METO, metoprolol; WT, wild type.

Cerebral arteries
It was first demonstrated in cerebral arteries that smooth-muscle contractile and dilator mechanisms are not affected by either dyslipidemia or ivabradine. Endothelium-dependent dilation induced by acetylcholine was impaired in dyslipidemic mice compared with wild-type mice. The use of ivabradine completely prevented this impairment of vasodilatory capacity in cerebral arteries (Figure 4, page 425). H$_2$O$_2$ derived from eNOS is an important relaxing factor in cerebral mouse arteries. In wild-type and ivabradine-treated mice, the administration of catalase (which degrades H$_2$O$_2$) decreased maximal cerebral artery dilation, whereas it had no effect in untreated dyslipidemic mice (Figure 4). These findings show that ivabradine protected cerebral arteries from undesirable changes induced by dyslipidemia.

Superior effects of ivabradine compared with the β-blocker metoprolol
Treating dyslipidemic mice with metoprolol reduced heart rate to the same extent as ivabradine (Figure 5A, page 425). In contrast, ivabradine provided superior preservation of endothelial function in renal and cerebral arteries in dyslipidemic mice compared with metoprolol. In renal arteries, metoprolol did not increase renal artery sensitivity to acetylcholine to the same extent as ivabradine (Figure 5B). In cerebral arteries, metoprolol did not prevent the decrease in dilator response to acetylcholine seen in dyslipidemic mice, unlike ivabradine (Figure 5C). The mitigated effects of metoprolol may be related to the coupling between endothelial β-adrenoceptors and eNOS.

Conclusion
Pure heart rate reduction with ivabradine prevents deterioration of the endothelial function of renal and cerebral arteries in dyslipidemic mice to a greater extent than the β-blocker metoprolol. Changes in endothelial function may represent the link between changes in heart rate and cardiovascular events. These results support the evaluation of the effects of ivabradine on clinical outcomes in patients with coronary artery disease or with cardiovascular risk factors.


Keywords: endothelial dysfunction; heart rate; coronary heart disease; cardioprotection; ivabradine
A TOUCH OF FRANCE

Under this heading, each issue of Medicographia features two cultural articles. The first one touches on the history of medicine, based around great figures from French history, while the second one addresses broader aspects of France’s heritage, such as history, art, literature, and the description of museum collections.

The heart of the kings of France: “cordial immortality”

C. Régnier, France

Reliquary from the end of the 18th century representing the Sacred Heart of Jesus and Mary’s Immaculate Heart.

© MuCEM, Dist. RMN/Virginie Louis/Anne Maigret.

The Cathedral Basilica of Saint-Denis

I. Spaak, France

Brilliantly colored stained glass windows in the Basilica of Saint-Denis depicting scenes from the Bible.

Copyright © Robert Holmes/CORBIS.
Commencing in the 13th century, the very catholic French sovereigns had their hearts, bowels, and internal organs (including the brain) separated from the rest of the body at death. A ritual ceremony was set up to glorify the royal organ, which was a symbol of political power and the people’s religious fervor. For all that separation, the body, the bowels, the internal organs, and the heart were interred in the same tomb. The ritual of separating the heart at death reached its peak in the 17th century: luxurious cardiotaphs (heart tombs) were created, funeral orations, and the appearance of grand ceremonies for heart burials, with specific testaments to the organ. In the debate opposing soul and body, the magnificence of the heart tombs contrasted greatly with the modesty of the funeral plaques covering the royal remains. Practiced not only by the kings of France, blood princes, and the French high nobility, separate heart-burial was also the custom for Polish, Scottish, and Austro-Hungarian nobility, as well as civil dignitaries and prelates of the Catholic Church. From the death of Hugues Capet in 997, the bodies of the kings of France (except three) were buried in the Basilica of Saint-Denis, but the hearts were meted out to different destinations according to the deceased sovereign’s will. Many were placed in the Church of the Annunciation in Paris. Spreading the royal hearts throughout the territory was a way for the French monarchy to make their political mark on the entire land.

The heart, mentioned 85 times in the Bible (figuratively), is for Christians a symbol of immortality, purity, suffering, and love. The sixth wound of Christ, interpreted as the impiety of man, injures the heart. In the Christian Occident, “cardiac cults” were established in the 13th century, such as that of Mary’s Immaculate Heart and the Sacred Heart of Jesus. Placing the soul in the heart, the Christian Occident symbolically assimilated the organ with immortality and with communication between men.1-3

In the context of “cordial” or “heart-related” religious fervor, it is not surprising that the kings of France, monarchs by divine right, attached particular importance to the preservation of their royal hearts. Extracted from the rest of the body, the heart often traveled to destinations (and fates) that differed from the corpse. This practice of separating the heart (and entrails) was vested with strong political and religious symbolism: the King gave his heart to France and offered his soul, his valor, and his purity to the devotion of the people. Symbolizing love and courage, the roy-
The ritual heart burial of the kings of France was a rather “coded” affair and always took place at night under cover of darkness. The heart was put into a reliquary, set upon a black taffeta–covered cushion, and then placed on the lap of the king’s confessor. The relic was thus transported in a funeral procession comprised of a black funeral coach drawn by six horses, escorted by twelve torch-bearing riders.

The postmortem fate of the body of Francis II

Born in Fontainebleau on January 20, 1544, Francis II was the eldest son of Catherine de Medici (1519-1589) and King Henry II (1519-1559). In 1557, aged 13, the young prince married Mary Stuart (1542-1587), the very Catholic Queen Mary I of Scotland whose beauty, refinement, and tragic destiny has inspired many writers. Francis II succeeded to the throne of France upon the death of his father in 1559, yet reigned a mere 17 months, mainly under the influence of his wife’s uncles (François and Charles de Guise).

Of fragile health, Francis II succumbed at the age of 16 to what was presumed to be meningitis following a chronic middle-ear infection. In his World History From 1550 Until 1601 (Histoire universelle depuis 1550 jusqu’en 1601), the Calvinist writer Agrippa d’Aubigné (1552-1630) wrote: “The son of Catherine de Medici was one of those whom we call “malnez,” unable to purge by the nose, or by the mouth, which he held open to get air, upon whose ear an abscess formed.”

Régnier de la Planche, historian of Francis II, recounted that the young prince spoke with a nasal voice and had a certain degree of deafness. A portrait in enamel made by Léonard Limosin in 1553, preserved at the Louvre museum, depicts a child with a swollen and pale face, a wide mouth, and a pug nose. Particularly inspired by the image, the doctor Augustine Cabanelès (1862-1928), an avid lover of the medical-historical footnotes of history, gave the following icono-diagnostic: “difficulty getting rid of accumulated mucus by nose and mouth, nasal voice, middle-ear inflammation, hardness of hearing, these signs are not themselves a grouping we consider characteristic of the presence of adenoid vegetations in the nasal pharynx, and how not to recognise the adenoidal features there?”

Cabanès took up the thesis of Doctor Potiquet, author of an 1893 work dedicated to the “Death of Francis II” (Mort de François II), and the doctor who concluded the relocation between adenoid vegetations and otitis media. Other more or less well-supported diagnoses were put forth, such as nasal polyposis, tuberculous osteitis, or syphilis (like his grandfather Francis I!).

On November 15, 1560, the young king fainted in the Church of Saint-Aignan in Orleans and was subsequently transported to the residence of Jérôme Groslot, town bailiff. Complaining of violent pains in his left ear, the king also had a high fever and a facial rash. The presence of the great surgeon, Ambroise Paré, during those painful days is uncertain; a vesicatory would have been applied behind the king’s ear as the usual treatment.

Would Catherine de Medici and Mary Stuart have been opposed to the trepanation of the king? On December 5th, Francis II, “this king without vice and virtue,” died. An inevitable rumor of poisoning surfaced, accusing the Huguenots, notably Prince Louis de Condé who was ousted from power by the Guises and condemned to death. Rumors surmised that the Protestants could have used a servant to poison the king’s nightcap or that Ambroise Paré could have put poison into the affected ear! Catherine de Medici was also suspected of wanting to get rid of her elder sons in order to exercise power alone. Though Francis II had not yet been buried, his brother, Charles IX (1550-1574), aged 10, was immediately enthroned. The haste was intended as a way of preventing the prominent men of the kingdom from stirring up trouble. No official ceremony was organized for the young king’s funeral.

The heart of the kings of France: “cordial immortality” – Régnier
In keeping with the tradition held by the kings of France since the Middle Ages, the heart was separated from the body at death and embalmed apart. The remains of Francis II were brought to the Basilica of Saint-Denis, while his heart was taken from the Chambre Ardente of the Hôtel Groslot to the Saint-Croix Cathedral of Orleans. The transfer ceremony for his heart took place in complete anonymity on December 6th, with neither members of the royal family nor dignitaries of the Kingdom or Church in attendance. Only three people accompanied the young king’s heart to its resting place: Sansac and Labrosse, the child’s tutors, and Louis Guillard, the Bishop of Senlis.

At the Cathedral of Orleans, where fragments of the cross and nails from the Passion of Christ are preserved, the heart was placed in front of the main altar. The elegant monument for the heart of Francis II was created by Fremyn Roussel and Jean Le Roux (aka Picard) and is comprised of a white marble column interspersed with flames and decorated with three funerary spirits. Two of these spirits are represented standing, extinguishing the flames of discord (etymologically, the disharmony or poor understanding of hearts!), while the third is depicted as seated reading a biblical text. At the top of the column, an urn of gilded bronze, crowned by the figure of a child’s face, was made to preserve the precious heart.

The monument to Francis II is now found in the Basilica of Saint-Denis near the column of his third brother, Henry III, who was assassinated in Saint-Cloud in 1589. In 1562, the civil unrest that had been smoldering finally burst into the flames of civil war. The cities of the Loire fell into the hands of the Protestants, and Orleans was conquered by the Prince de Condé. The heart of Francis II was exhumed, “fricasseed and burned” in a big bonfire by the hordes of people who then devastated Notre-Dame de Cluny, where they overturned the tomb of Louis XI (1423-1483), one of the rare French sovereigns opposed to the separate burial of his heart.4,7,8

---

4. The heart of the kings of France: “cordial immortality” – Régnier

A TOUCH OF FRANCE

Medicographia 101 Regnier:Mise en page 1 1/09/09 12:59 Page 432

The cover of the “Treaty of Embalming” (Traité des embaumements), written in 1699 by Louis Pénichet, describing the techniques for preparing a heart for burial.
The heart of the Green Gallant: from assassination to bonfire

Henry IV (1553-1610), age 57, was assassinated in Paris in the Les Halles market district on May 4, 1610. The king wanted his heart to be placed in the school church of La Flèche, in the modern department of Sarthe. In accordance with his wishes, the Queen, Marie de Medici (1573-1642), had the relic taken to the Jesuits who organized a solemn ceremony. Accounts from the time describe the translation ceremony of the murdered sovereign’s heart in minute detail.

On May 6, the monks of the Saint-Louis Church in attendance at the embalming of the king’s heart reported: “Monsignor the Prince de Conty, collapsing into tears, knelt down in front of the royal heart and, his prayers finished, having taken it from a cushion adorned with gold brocade, put it back into the hands of the Jesuit superior.” The heart of Henry IV was displayed for 3 days at the Saint-Louis Church in Paris.4,7,9

A 1699 work called the Treaty of Embalming (Traité des embaumements), written by Louis Pénichier, described the techniques for preparing a heart for burial in detail: opened and cleaned, the heart was put into spirit of wine or oil of turpentine to soak. Dried, covered with plants and aromatic tinctures, the heart was then put into a small oilcloth bag and sealed inside a lead box before being placed into its reliquary.4,6,7

Escorted by 12 horsemen bearing torches, the heart of Henry IV left Paris on May 9th in a black coach drawn by six horses outfitted in funeral harness. Put in a reliquary, the sacred organ was placed on a black velvet cushion, which rested on the lap of Father Cotton, the King’s Confessor. The funeral procession, commanded by the Duke of Montbazon, passed through Nogent-le-Rotrou, La Ferté-Bernard, and Le Mans, with an overnight stop in Chartres, where Montbazon had arranged for the heart to spend a night amidst the hearts of other royal ancestors. Along the route from the beginning to the end of the journey, the grieving crowd paid ardent tribute to the heart of Henry IV: “They shed more tears than if they had lost their fellow loved ones.” Tradition permitted people to approach and kiss the relic during its passage: nobles kissed the box, commoners and peasants kissed the cushion. The funeral procession took 9 days to reach its destination.4,6,7

Passing under a triumphal arch, the procession arrived in La Flèche on May 18th. The royal organ was...
placed on a marble pyramid in the choir of the Church of Saint-Thomas. The four faces of the pyramid were made to represent the four virtues of the late sovereign: piety, swiftness of mind, courage, and clemency. Father Cotton delivered the funeral oration: “Where then Sirs, will this divine heart take its rest? Below ground in some gloomy cavern which makes us shudder? No, no, Sirs, he needs a living and breathing tomb; and as long as only one of this company remains on earth, he will rest, he will live in our court, he will be lodged in our memory.” In front of a huge kneeling crowd, Father Cotton took the heart between his hands and said: “Here lies the heart of Henry the Fourth, the very high, very powerful, and very Christian King of France and Navarre” and repeated three times according to custom: “The king is dead, pray for his soul [his heart].” The ceremony ended with the sound of trumpets and “cries” of the people wishing long life to the new king, Louis XIII.

The tomb of Henry IV’s heart was located high up, near the vaulted arch, a placement that Father Cotton justified:

It must be in view of everyone, raised in the holy and sacred temple of God with whom his soul reigns in the Heavens, and that one says upon entering: Here is the heart of the great Henry, Henry the Happy, Henry the Valiant, Henry the Brave, Henry the Wise, Henry the Gracious! Here is the heart of the Father of the French, Protector of the Innocent, Premier Monarch of the world. Here is the heart of France that rests in this place of his choosing, in order to safeguard the good and shield from the villains.

While alive, the king had been preoccupied with his burial and ultimately wished to have his crowned heart surmounted by his bust and surrounded by allegories representing Force and Justice.

The heart of Henry IV was joined by that of the queen in February 1643 (who probably died as a consequence of heart failure).

In 1793, the church of La Flèche became a political club, but the presence of the royal relics ruffled the Republican fiber of the Montagnard, Didier Thirion (1763-1815), who ordered the burning of both royal hearts in public. According to Augustine Cabanès, doctor and author of the famous series The Secret Office of History (Le cabinet secret de l’histoire), the ashes of the fire were supposedly gathered up just after the ceremony by a man named Boucher, correspondent member of the Royal Academy of Surgery. Said to have been put into a bottle with the inscription Cineres cordis Henrici Magni, the ashes were never found...

The heart of Louis XIV: an unexpected destiny

Louis XIV (1638-1715) died from gangrene of the left leg (linked to diabetes?) in Versailles on September 1, 1715. According to tradition, the remains of the sovereign were interred in the Basilica of Saint-Denis. To respect the king’s final wishes, the heart was given to the Jesuit Superior from the Saint Paul-Saint Louis Church on rue Saint Antoine in Paris, where a chest crowned with two silver and bronze angels supporting a silver heart had been built to contain the hearts of both sovereigns, Louis XIII (1601-1643) and Louis XIV.

On September 15, 1792, at the request of the Mint, the reliquaries were melted down. Both royal hearts were sold to Alexandre Pau, also known as Pau de Saint-Martin (1751-1820), a wildlife and landscape painter, whose paintings can be found in Sceaux, Toulouse, Dunkirk, and Rouen. Another painter, Drolling, acquired the hearts of Marie Therese, the Duchess of Burgundy, and the Regent. Though difficult to obtain, painters needed to use mummified organ matter, which they ground and combined with some oil in order to get a nice...
brown color, called “mummia.” Only a fragment of the heart of Louis XIV (which was the biggest?) would have been used by Saint-Martin for his works. During the Restoration, on March 3, 1819, the painter gave a piece of the Sun King’s heart and the unused heart of Louis XIII to the Count de Pradel, the minister in charge of the royal household of King Louis XVIII (1755-1824), in exchange for a snuff-box. The relics were put in copper caskets and placed in the Basilica of Saint-Denis. Another legend says that the heart of Louis XIV was brought to the Val de Grâce Hospital.4,7

In an 1994 article appearing in the Bulletin de la Société Libanaise d’Histoire de la Médecine (Bulletin of the Lebanese Society for the History of Medicine), Jean-François Dars and Ann Papillault deciphered a painting by Saint-Martin made after 1793, entitled Vue de Caen (View of Caen), which is located in the museum of Pontoise. Both authors wondered: “The dark red color used for the garments of the figures in the forefront, could it be from the heart of Louis XIV?” Just a tiny sample of the canvas would make it possible to identify the royal DNA...

Cabanès provided a tragic-comic version of the fantastic adventure of the heart of Louis XIV: an English doctor, Doctor Buckland, residing at 104 rue du Faubourg Poissonnière, was called upon (when? why? by whom?) to examine the heart of the Sun King. Partly naming his sources, Cabanès wrote: “It was something dry and shrivelled, greatly resembling a piece of leather. The learned doctor examined the thing with rapt attention, and sniffed it for a long time, so long that he ended up swallowing it!” The body of Doctor Buckland rests in Westminster Abbey. The mystery remains, is the heart of the great King in Val de Grâce, on the canvasses of Saint-Mart in, in the Basilica of Saint-Denis, or in Westminster Abbey?4,7

The heart of Louis XVII: a tenacious mystery?

Louis Charles, Duke of Normandy, the second son of Louis XVI and Marie-Antoinette, was born in Versailles on March 27, 1785, and became Dauphin on June 4, 1789, after the death of his elder brother (who died from osseous tuberculosis contracted from his nursemaid).

Along with his family, the young prince was incarcerated in the Temple Prison on August 12, 1792, and then separated from his father on December 11th. The child was described as healthy, without any particular medical antecedents, and rather chubby-cheeked.

After the execution of his father on January 21, 1793, Louis XVII became king. Torn away from his mother on July 3rd, the young child was put into the care of Simon the shoemaker and his wife, who were instructed to raise him according to the principles of the Republic. His mother, Marie-Antoinette, was transferred to the Conciergerie on August 1st and guillotined on October 16th.7,11 In January 1794, the young Capet was taken from the Simons and abandoned into the hands of other “jaillers” in exchange for a discharge attesting to his good health. The mystery of Louis XVII began at this precise moment in time: the childminders were changed often and did not really know the child. The famous surgeon, Joseph Desault (1738-1795), appointed by the Convention to treat the young prince, entrusted to his nearest and dearest that he did not recognize the child whom he had seen before the Revolution. Very conveniently, Desault died on June 1, 1795, from typhoid fever (or, according to his wife, from poisoning).7 What became of the royal heir? For some, the young Capet died in the Temple on June 8, 1795, in a state of advanced cachexia (tuberculosis?). For others, he escaped (perhaps with the assistance of his former caregiver Mrs Simon?) and was replaced by another (older) child. Historians, Legitimists, and Orleanists held opposing opinions on this question, which rapidly took on the elegant allure of an enigma highlighted with improbable developments.
In order to hush up the rumors of poisoning, the members of the Convention hastened to order an autopsy on the child who died in the Temple. On June 9, 1795, Doctor Philippe-Jean Pelletan, Doctor Jean-Baptiste Dumangin, Doctor Pierre Lassus, and Doctor Nicolas Jeanroy performed the autopsy. “We found in a bed the corpse of a child who seemed to us to be approximately ten years of age, that the commissioners said was the deceased Louis Capet, and whom two of us recognized as the child to whom they had administered treatments for several days.” The doctors were careful not to officially authenticate the corpse of Louis XVII and failed to take note of the many scars the child had had since birth, even though Lassus was the Professor of Forensic Medicine in the medical school of Paris. Death was attributed to a “long-term scrofulous defect”; this term indicating osseous tuberculosis.7,11

On the 10th, or perhaps the 12th June, the corpse of the child from Temple Prison was buried in the mass grave of the Saint-Margaret Cemetery on rue Saint-Bernard in Paris. The gravedigger, a man by the name of Bertrancourt, removed the corpse from the communal grave, put it into a lead coffin, and then buried it elsewhere in the cemetery.

The skeleton from the Saint-Margaret Cemetery in Paris was exhumed in 1846. Examined by Doctor Joseph Récamier (1774-1852) and Doctor Gabriel Andral (1797-1876), the examination confirmed osseous tuberculosis in a 16-year-old boy. Exhumed again in 1894, the skeleton was examined by the doctors Magitot and Manouvrier, reputed paleo-pathologists, who identified a subject between 18 to 20 years of age. Two obvious conclusions were drawn: either the exhumed skeleton was not that of the Dauphin, or the child who died in the Temple was not Louis XVII. The examination of the bones was inconclusive; however, a relic has managed to be preserved to this day, albeit through numerous adventures: the heart presumed to be that from the child who died in the Temple Prison...7,10,11

During the autopsy in 1795, Doctor Philippe-Jean Pelletan (1747-1829), professor of the surgical clinic at the Hôtel-Dieu, appropriated the heart, which he then kept at home in a jar of alcohol. After the return of the Bourbons, the doctor wanted to restore the heart to the royal family. Fearing imposters, Louis XVIII refused this burdensome present just as many Louis XVII survivors revealed themselves. Likewise, the Duchess of Angoulême (sister of Louis XVII), Charles X, and the Count of Chambord, refused to accept this relic; did they perhaps doubt its authenticity?

In 1828, Doctor Pelletan gave the heart to Monsignor Hyacinthe Louis de Quélen, Archbishop of Paris, who kept it in the treasury of the Archdiocese Palace. On July 29, 1830, during the “Trois Glorieuses,” the Archbishop’s palace was vandalized. Rioters inadvertently destroyed the famous vase containing the heart of the Dauphin. On August 5th, once the July Revolution had ended, Gabriel-Philippe Pelletan (1792-1879) (son of the doctor who had removed the organ) and Lescroart, one of the rioters, went to the vandalized palace and there they found the heart on a heap of sand. Other accounts put this scene in February of 1831.7

In 1895, after having passed through many hands, the vase containing the “desiccated heart, held to the upper wall (of the jar) by a copper cylinder” was given to Count Urbain de Maille, representative of Don Carlos, the Duke of Madrid, pretender to the throne of France. The relic was brought to the Froschdorff Chapel, near Vienna, in a blood-covered
shawl, which Marie-Antoinette wore to the scaffold. In 1930, pertaining to the relic, the famous doctor-historian Augustine Cabanès wrote:

Were it proved that the heart in dispute belonged to a 10 to 11-year-old child, it would still be necessary to show that this child is indeed the Dauphin. And the misfortune is that all hearts from 10-year-old children are alike, more or less, and that nothing enables one to differentiate between the heart of the Dauphin of France and the heart of a peasant...

In 1975, the Massimo princesses, young daughters of Don Carlos, gave the relic to the Duke of Bauffremont, president of the Memorial of France in Saint-Denis so that the (presumed) heart of Louis XVII could be preserved in the necropolis of the Kings of France, where it now rests.11

In December 1999, according to journalist-historian Philippe Delorme, biologists from the University of Louvain and the University of Münster (Germany), after being given permission by the Duke of Bauffremont, removed (in front of bailiffs) four fragments of the presumed heart of Louis XVII. The tissues were “desiccated, contracted, and of a petrified consistency.” Cut up with the aid of a saw, the fragments were taken from the cardiac apex and near the aortic orifice. Professor Cassemán (Louvain) explained:

We were unable to penetrate it with a scalpel. It was therefore decided to use a small sterilised saw with which the top of the heart and the end of the aorta were cut. We then saved these pieces again to get two samples. One was for us in Louvain, the other for the University of Münster. Following that, each person worked on his part.

The very damaged mitochondrial DNA (non-nuclear) contained in the fragments of the heart of the Dauphin was compared with the hair of Marie-Antoinette, her two sisters, Anne of Romania, and André de Bourbon Parma.

On April 19, 2000, the professors Jean-Jacques Cassemán and Bernd Brinkmann (Münster) came to the same conclusion: all of the genetic samples had “a genetic consensus sequence” in common. Using polymerase chain reaction amplification technology, the researchers highlighted an identical alignment of sequences in the D loop of mitochondrial DNA. In his conclusions, Professor Cassemán remained cautious: “As a scientist, I cannot maintain that this is Louis XVII. It is up to the historians to bring proof of that. All that I can say is that the heart which we examined comes from a maternal descendant of Marie-Antoinette.” Convinced by the results of the genetic analysis, Louis de Bourbon, Duke of Anjou, pretender to the Throne of France, declared: “today marks the end of more than two centuries of mysteries.”11


The unlikely history of the young Capet could have come to an end with scientific evidence, but several methodological protests were raised: (i) the exclusively maternal transmission of mitochondrial DNA was called into question; (ii) the analysis of the simple strand of hair without the follicle would be very inconclusive because the analyzed hair of the ancestors and descendants of Louis XVII did not include the follicle; and (iii) the heart from Pelletan did not present any proof of authenticity...

Epilogue

Louis XVI, decapitated on January 21, 1793, did not have the privilege of a body and heart funeral. He had, however, dedicated his reign to the cult of the Sacred Heart and wrote to his confessor, Father Hebert, at the beginning of 1792: “You know, my God, that my heart always submitted to faith and moral rules; my mistakes are the fruit of my weaknesses.”4,12

Assassinated on July 13, 1793, Doctor Jean-Paul Marat, spokesperson for the Montagnards of the Convention, did indeed have the privilege of a ceremony of the heart. His body was displayed in the Church of the Cordeliers from July 15th. His corporeal remains were brought to the Pantheon on July 21st and then removed in 1795. His heart was locked in a pyxis (urn) and brought to the Cordeliers. The heart was put on display at the Luxembourg Palace on July 21st then returned to the Cordeliers on July 28th, where it was hung in the vaulted arch above the meeting table of the Revolutionaries. At Libreville (Saint-Denis), with the rest of the royal tombs from the Basilica, a section of cave was prepared in order to house Marat’s heart.4,13

Conclusion

The writings of Cabanès often oscillate between more or less referenced historical truth and imaginary accounts. Contrary to his affirmations, the Basilica of Saint-Denis does not have “the famous cabinet where the hearts of Henry IV, Marie de Medici, Louis XIII, and Louis XV are presumed to be locked away.” According to the curator of the Basilica, the Chapel of the Princes, located at the entrance of the crypt (southern arm of the transept), has nine lockers containing fragments of the bodies of Marie de Medici, Henry IV, Louis XIV, and the hearts of Louis XIII, Louis XIV (segmented), Louis XVIII, and the Duke of Berry (second son of Charles X).
A TOUCH OF FRANCE

References


LE CŒUR DES ROIS DE FRANCE : « IMMORTALITÉ CORDIALE »

The Cathedral Basilica of Saint-Denis is situated north of Paris on the 3rd-century burial site of the holy martyr Saint Denis. From its beginnings as a shrine in the 4th century, it developed into a basilica that became the definitive royal resting place in the 10th century. Further development by Abbot Suger in the 12th century made it the premier example of Gothic art, and after repeated pillaging in the 15th and 16th centuries, it was eventually restored and elevated to its current cathedral status in 1966.

Considered the first monumental masterpiece of Gothic art, the Basilica of Saint-Denis was constructed north of Paris on the site of a Gallo-Roman cemetery where the holy martyr, Saint Denis, had secretly been buried in the latter half of the 3rd century. A shrine erected there in the 4th century was used as a place of pilgrimage, which developed into a monastery in the 5th century. Dagobert became the benefactor in the 7th century and founded a basilica, after which the monastery became one of the main Merovingian burial sites. Pepin the Short was anointed king in the monastery in the year 751. The basilica became the definitive royal resting place with the death of Hugues Capet in the 10th century. It continued to develop, and proceeded to become one of the most powerful Benedictine abbeys of the Middle Ages. Abbot Suger, an influential political figure and remarkable administrator, had the structure rebuilt according to new architectural techniques in the 12th century, and thus emerged the Gothic features of the abbey. The use of rosette windows and cross-ribbed arches filled the building with light. Further construction work in the 13th century served to give the Basilica its current appearance. A sacred place for the French monarchy, and the necropolis of the kings of France, the French Revolution precipitated its decline. Through the guidance of Viollet-le-Duc, the Basilica was carefully restored in the 19th century. The abbey church was granted cathedral status in 1966, and today the edifice houses an exceptional collection of recumbent effigies and tombs from the Middle Ages to the 16th century, as well as stained glass windows from the 12th to the 19th centuries.

On their marble resting place, two pairs of bare feet, toes stretched skyward, mark the tomb of Francis I. Dazzled by the majesty of the transept, the rosette window, the height of the central nave, and the immense walls of colored glass stretching above the monumental choir, a visitor entering the Cathedral of Saint-Denis by the south entrance might miss the soles of the sovereign altogether, and head for the double ambulatory.

If, however, the visitor neglects the recumbent effigy of the Victor of Marignan and his wife, both lying under their stone arch, they will definitely be deprived of a vital prelude to what awaits. Brutally nude, the bodies mark the beginning of a succession of emotive displays punctuating the royal necropolis, including the moving memorial of Louis XVII, a child of whom nothing remains but a pebble-sized heart dis-
played in a transparent urn. The splendor of the building, the silence of the crypt, the magnificence of the nave, and the exceptional funerary art serve as a reminder that the Cathedrall Basilica of Saint-Denis is not only a Gothic masterpiece, but also the result of the evolution from simple shrine to admired abbey to powerful basilica, as well as a royal necropolis that illustrates the antinomic relationship between power and death.

The vanity of existence and royal power

The tomb of Louis XII (1462-1515) and Anne of Brittany (1476-1514) was the first of its kind. The commission for the tomb was given to Guido Massoni and Jean Juste, two Florentine artists residing in Tours. A majestic piece of architecture, the Carrara marble mausoleum stands on two levels in the north transept of the cathedral. In the lower part, emaciated bodies, marked by convulsions and spasms of death throes, are a reminder of the fatal destiny of the body. The queen’s head is thrown back as though trying to catch a last gulp of air. The king’s half-open mouth appears to evict a last death rattle. Crumpled and askew sheets call to mind sweat, a battle, and foul odors. Breasts fall, ribs protrude, and the frightfully distended veins of the neck look ready to burst. Nothing is spared in both funerary effigies, not even the roughly sewn up belly, which was opened for evisceration prior to embalming. Standing in full contrast to the lower level, the upper storey of the monument depicts Louis XII and Anne of Brittany in all their plenitude. Wearing long cloaks, heads bare of crowns, there is no ostentatious sign of power. The sovereigns are shown kneeling in front of their modest cushion-covered individual altars. With their hands entwined, they pray for resurrection.

Battle scenes on the base illustrate the hours of glory of the king’s reign and the final victory of death. Black marble allegorical representations, located in the four angles of the monument, praise the Cardinal Virtues.

More than a commemoration of the departed, the representation of both states of being—dead and alive—offers Christians a meditation on the meaning of life and accentuates the continuity of royal power in spite of the brevity of existence.
Presented under an imposing triumphal arch constructed in 1547 in the ancient style, the “transi” or transitory tomb of Francis I and Queen Claude of France was laid out in monumental tradition characteristic of the Renaissance. On the tomb is a relief from the same inspiration as that of Louis XII and Anne of Brittany. The sovereigns are represented in their original naked state under a marble canopy. Shown in prayer, accompanied by their three children on the upper platform, the scene exudes the power of royalty.

The collection of funerary statues and tombs in the Basilica Saint-Denis has been augmented by monuments brought from the abbeys of Sainte-Geneviève, Saint-Germain-des-Prés, and Royaumont, as well as convents of the Cordeliers, Jacobins, Celestines, and other religious orders.

The tombs of the son of Clovis I, Childebert I (558 AD), Chilperic (584 AD), and his wife Fredericund (597 AD) were originally made for Saint-Germain-des-Prés, but having been desecrated, their remains were moved and portions of their tombs remade in the 12th century. Dating from 1150, the effigy of the Frankish king resting at the bottom of a sarcophagus is one of the nicest Parisian productions from the middle of that century. The unique stone celebrating the queen is the original, and the slab is inlaid with a mosaic of colored stones and slender threads of gilded copper. These works were commissioned by the monks in memory of the couple who chose to be buried in their abbey.

In this abbey church turned cathedral, which serves as the resting place for 42 kings, 32 queens, 63 princes and princesses, and 10 prominent figures of the Kingdom of France, the contrast between funeral traditions is gripping. What connection is there indeed between the pompous and lofty Renaissance architecture and the simple pit in which the remains of Saint Denis were buried? A hole dug in the same soil…

From shrine to cathedral by way of a tomb

The first structure erected on the site of the Gallo-Roman graveyard containing the tomb of Saint Denis, first bishop of Paris who was martyred circa 250 AD, was a simple shrine. A place of pilgrimage, the first abbey-church was constructed in the 5th century. During the reign of Clovis (481-511) the abbey was chosen as the sepulcher for the remains of the Frankish aristocracy. Enlarged in the 7th century through the impetus of Dagobert I (639 AD) who was buried there, followed by his son Clovis II (657 AD), the monastery quickly became one of the main burial sites for the Merovingian dynasty. From the time of Hugues Capet (987-996), the basilica was firmly established as the definitive “cemetery of the kings.”

In the 12th century, Abbot Suger, adviser of Louis VI and Louis VII, considerably developed the connections between the Sandoysien cult and the monarchy. A remarkable administrator, Abbot Suger made the abbey his chief work from 1122 until the year of his death in 1151, and the result was the premier representation of Gothic art worldwide. The use of rosette windows and impressive cross-ribbed vaulted arches gave the church a wide-open, airy feeling, and filled the
church with light. The combination of internal ornamentation, surges of gold, painted decorations and gemstones, and the stained glass windows united to shower praise on the liturgy. New construction work carried out in the 13th century, under the reign of Saint Louis, gave the basilica its current appearance.

In addition to war and plundering, the French Revolution contributed to the Basilica Saint-Denis’ decline and eventual abandonment. Revolutionary soldiers desecrated the tombs, and the roof was destroyed in order to get to the lead. As Chateaubriand wrote in his work, The Genius of Christianity (Génie du Christianisme), “Saint-Denis is deserted. The bird uses it for passage, the grass grows on its broken altars, and one can no longer hear the raindrops which fall from the bare roof.” Napoleon decided to have the monument restored in order to “consecrate the burial of the Emperors.” Louis XVIII made the Basilica his vocation. He ordered searches and excavations in the Valois cemetery on the north side of the abbey, with the aim of recovering the royal remains that had been strewn about by the revolutionaries. Restored by Viollet-le-Duc from the year 1846, the basilica became a cathedral in 1866.

Burial of a martyr
Saint Denis, the patron saint of France, is considered the first bishop of Paris (Lutecia). He died as a martyr in the latter half of the 3rd century, circa 258-280. Denis (or Dionysus), was a disciple of Saint Paul. After the apostle’s death, Pope Clement I sent him on a mission to Gaul (circa 250) accompanied by his two companions, Rusticus and Eleutherius. There they perished as victims of an edict ordered by the Roman Emperor Decius to suppress and persecute Christians. Imprisoned and tortured, the saints were finally decapitated on the highest hill in Paris, the Butte of Montmartre. According to legend, Denis miraculously picked up his head, which had been cut off with an axe, and started walking, continuing to sing hymns and preach sermons. He carried his head for several kilometers, to near the village of Cattilacus (Catolacus).

Roman soldiers were given the mission of throwing the bodies of the saints into the Seine; however, a pious woman by the name of Catulla, who was also a follower of Denis, distracted the soldiers from their task. She managed to inebriate them, then recovered the bodies of the saints and buried them in a nearby field, where the quickly growing wheat kept them hidden.

Around the year 331, the date of Constantine’s edict imposing “Peace of the Church,” a small chapel was built as a shrine on the burial site. Thereafter in the 5th century, a church of approximately 60 square meters was constructed to replace the shrine, and a monastery was later established. The abbey church was continuously enlarged and improved upon until the 13th century. Similarly, over the centuries, both the Dionysian cult and the abbey acquired considerable importance.

Royal sepulcher
The abbey was chosen during the reign of Clovis (481-511) to serve as the sepulcher for the Frankish aristocracy. Queen Aregund, who died around 580, was the great grandmother of Dagobert and the first royal to be buried in the Church of
Saint-Denis. For her last sleep, she was dressed in silks from Constantinople and adorned with earrings, garters, and gold brooches inlaid with garnet. Treasures in accordance with her rank, they testified to the importance granted to a sanctuary in the Early Middle Ages.

Fleeing his father Clothar, Dagobert had an apparition while in Catulliacum. According to legend, the martyrs appeared and promised to help him if he committed to building a church that Christ would personally dedicate the evening prior to the official consecration. Dagobert accepted and through his impetus, the existing church was enlarged and a basilica was built. He is sometimes considered—wrongly—to be the founder of the monastery. Dagobert was the first king to be interred in the basilica in 639 and the monastery rapidly became one of the main and true burial places for the Merovingian dynasty. The son of Dagobert, Clovis II (657 AD), was also buried there. From that time on, the kings conferred upon Saint Denis the title of “special patron,” a title that was confirmed by the Carolingians and then the Capetians.

Throughout the course of history, sovereigns were always in search of legitimacy, which partly explains the desire to be laid to rest near the relics of Saint Denis, Saint Rusticus, and Saint Eleutherius. The strength and might of the martyrs was thought to help them acquire power and protection during their life—especially in battle—and according to belief, would enable their direct ascent to Heaven after death. Be that as it may, the abbey suffered a few “rejections” and “abandonments,” with some royals choosing intern-

ment elsewhere; for example, in the Basilica of Saint-Germain-des-Pré. Known at that time as the Church of Saint-Vincent with an adjoining abbey, Sainte-Croix, the original structure was founded by Childebert I, son of Clovis I, as a shrine to house Merovingian relics. Several Merovingian kings and their families were interred there, such as Childebert I (558 AD) and his wife and family, as well as Chilperic (584 AD) and his wife Fredegund (597 AD).

On the other hand, some sovereigns, such as Charles Martel (741 AD) vowed particular devotion to Saint Denis, and asked to be laid to rest in the abbey church. His son, Pepin the Short, or Pippin III (768 AD), the first sovereign of the Carolingian dynasty, was anointed king in a lavish ceremony at the monastery in 751. A few years later, in 754, he expressed his wish to be interred there. He also vowed to rebuild the ancient basilica. Meeting his end during a military campaign in 768, Pepin’s corpse was returned to Saint Denis. According to his wishes and as a sign of humility, he was buried outside the entrance of the west porch, face down, apparently for the sins of his father.

The work undertaken by Pepin’s two sons, Charlemagne and Carloman I, was started only after his death, circa 768-769. On February 24, 775, Abbot Fulrad dedicated the new building, comprised of one immense nave divided into three by two lines of marble columns, a transept and an apse, all in all measuring more than 80 meters long. The structure was grandly lit by 1250 lamps during big celebrations. In approximately 800, Abbot Fulrad endowed the basilica with a new addition in front of the west facade above the tomb of Pepin the Short. As in Saint Peter’s Basilica in Rome, a crypt under the apse enabled pilgrims to venerate the relics.

On the other hand, some sovereigns, such as Charles Martel (741 AD) vowed particular devotion to Saint Denis, and asked to be laid to rest in the abbey church. His son, Pepin the Short, or Pippin III (768 AD), the first sovereign of the Carolingian dynasty, was anointed king in a lavish ceremony at the monastery in 751. A few years later, in 754, he expressed his wish to be interred there. He also vowed to rebuild the ancient basilica. Meeting his end during a military campaign in 768, Pepin’s corpse was returned to Saint Denis. According to his wishes and as a sign of humility, he was buried outside the entrance of the west porch, face down, apparently for the sins of his father.

The work undertaken by Pepin’s two sons, Charlemagne and Carloman I, was started only after his death, circa 768-769. On February 24, 775, Abbot Fulrad dedicated the new building, comprised of one immense nave divided into three by two lines of marble columns, a transept and an apse, all in all measuring more than 80 meters long. The structure was grandly lit by 1250 lamps during big celebrations. In approximately 800, Abbot Fulrad endowed the basilica with a new addition in front of the west facade above the tomb of Pepin the Short. As in Saint Peter’s Basilica in Rome, a crypt under the apse enabled pilgrims to venerate the relics.

On the other hand, some sovereigns, such as Charles Martel (741 AD) vowed particular devotion to Saint Denis, and asked to be laid to rest in the abbey church. His son, Pepin the Short, or Pippin III (768 AD), the first sovereign of the Carolingian dynasty, was anointed king in a lavish ceremony at the monastery in 751. A few years later, in 754, he expressed his wish to be interred there. He also vowed to rebuild the ancient basilica. Meeting his end during a military campaign in 768, Pepin’s corpse was returned to Saint Denis. According to his wishes and as a sign of humility, he was buried outside the entrance of the west porch, face down, apparently for the sins of his father.

The work undertaken by Pepin’s two sons, Charlemagne and Carloman I, was started only after his death, circa 768-769. On February 24, 775, Abbot Fulrad dedicated the new building, comprised of one immense nave divided into three by two lines of marble columns, a transept and an apse, all in all measuring more than 80 meters long. The structure was grandly lit by 1250 lamps during big celebrations. In approximately 800, Abbot Fulrad endowed the basilica with a new addition in front of the west facade above the tomb of Pepin the Short. As in Saint Peter’s Basilica in Rome, a crypt under the apse enabled pilgrims to venerate the relics.
However, it was not until 200 years later in 996, upon the death of Hugues Capet, the first Capetian monarch, that Saint Denis would become the definitive "cemetery of the kings," with few exceptions.

A visionary abbot

The 12th century was marked by the arrival of Abbot Suger. An exceptional character, adviser of Louis VI and Louis VII, Suger dedicated his life to the State and the Church, and confirmed the crucial role of the basilica. Abbot of Saint-Denis from 1122 until his death in 1151, he also assured the regency of the kingdom when Louis VII departed for the second crusade in 1147.

Inscribed on the scarlet banner, interspersed with the golden flames of the famous oriflamme of Saint-Denis, is "Montjoie! Saint Denis!" which became the battle cry of the knights and the slogan of the Kingdom of France, which was under the protection of the guardian saint. The standard is a pretty image of the personal union between the abbey, the patron saint, and the king. Systematically raised in times of war by the sovereigns, who would themselves collect it from the hands of the abbot from the altar of the holy martyrs, the standard is one of the main objects from the medieval era that evoked the first notions or feelings of "nation."

Suger showed himself to be an unparalleled administrator of the abbey. He started by having the basilica restored, repairing cracks and taking on painters from various regions to cover the walls with gold and precious colors. He accumulated enough funds to enhance the church's treasure and undertook the reconstruction of the façade and apse, while at the same time conserving the ancient Carolingian nave, which he maintained was the original from the first abbey church that, according to legend, Dagobert I constructed and Christ consecrated.

The worksite for the façade was set up again in 1130. Using the techniques and completely new aesthetics of Gothic art, he developed a complex architectural plan. The façade was conceived as a tribute to the Trinity and was comprised of two towers linked by a crenellated parapet symbolizing Heavenly Jerusalem. The decor of the three portals should be considered the birth of Gothic sculpture. The tympanum of the central portal represents Christ, who sits enthroned in the Last Judgment; He judges those who pass through the gates of heaven. The right portal shows the last communion of Saint Denis and his two companions. The tympanum of the left portal is dedicated to their martyr.

In 1140, although the towers were not yet completed, Suger began reconstruction work of the apse of the abbey church, which was completed in a record 4 years. The attention given to the fusion of space, and the double ambulatory divided by narrow columns shaped into one sole block in order to let light pass through, established the choir as one of the most beautiful achievements of the era. The external ambulatory opened onto nine adjoining chapels connected by wide
passageways illuminated by broad glass ceilings. As though floating in a glass cage, the apse reflects Suger’s spirituality, which was based on contemplation and the transcendence of light. The floor was covered with mosaics, which have since disappeared.

Gothic vocabulary

Thanks to Abbot Suger, Saint-Denis became the true sanctuary of the monarchy. The abbey church rivaled Reims, home of the sacred cathedral. Unfortunately, however, Suger would not be there to see the completion of his masterpiece. Reconstruction of the nave was interrupted by preparations for the crusade of Bernard de Clairvaux, and the abbot died on January 13, 1151. Meanwhile, the concepts and knowledge of his architecture gave birth to Gothic art. A new vocabulary was also born—window size, open walls, cross-ribbed vaults, and broken arches—which became more enriched with each successive generation.

Suger’s successors seem to have dedicated the second half of the 12th century to restoring the financial base of the abbey. It was not until 1230, under Abbot Eudes de Clémence, that they thought of completing the basilica, in agreement with the young Louis IX and his mother, Blanche de Castille, 

**NOT TO MISS**

- **South transept**: 14 recumbent statues (gisants) commissioned by Saint Louis circa 1263, the tomb of Charles V—The Wise, the first sculpted portrait in funerary history, tomb of Francis I.
- **Crypt**: Chapel of the Bourbons with cenotaphs commissioned in the 19th century, the heart of Louis XVII, the sarcophagus of Queen Aregund, first queen to be buried in Saint-Denis, burial place of the martyr saints, vault of the Bourbons with the remains of Louis XVI and Marie-Antoinette.
- **North transept**: the stained glass windows of the upper sections, the two-storeyed tombs of Louis XII and Anne of Brittany, Henry II and Catherine de Medici, the tomb of King Dagobert.
- **Apse**: the Merovingian kings and queens, the metal tombs of the children of Childebert and Fredegund, stained glass windows from the time of Abbot Suger.
- **Chapel Saint Louis**: the standard (oriflamme) and the praying figures of Marie-Antoinette and Louis XVI.
The building needed to compete with the most prestigious Gothic cathedrals in the north of France. The daring architecture of Suger’s plan was reinforced, the triforium and the high windows were reshaped, and the Carolingian church was razed. The transept was divided into five spans to make room for the tombs of the kings of France and the huge rosette windows of the transept, which served as models for the palatial chapel of Saint Germain-en-Laye and Notre Dame de Paris. These features firmly inaugurated the radiant Gothic style, a new architectural phase adopted throughout Europe. The nave was finally completed in 1281.

In May 1389, grand ceremonies were organized at Saint-Denis to rally the knighthood of King Charles VI, and the monks celebrated a mass in honor of Bertrand Du Guesclin, who was buried in the basilica in 1380. Then, abruptly, with the standard of Saint-Denis proving ineffectual against the English armies, relations between the abbey and the kingdom became strained. The church was pillaged again and again in the 15th and 16th centuries. From the time of Marie de Medici’s coronation in the church in 1610, ceremonies brought about modifications and depredations.

**Revolutionary madness**

On Friday September 14, 1792, the monks of Saint-Denis celebrated their last service in the abbey church. The following year, in the name of the New Republic, a group of Revolutionaries invaded. From October 12-25, 1793, the royal remains were exhumed and thrown into a mass grave in the Valois cemetery on the north side of the building. “Most of the bodies were decaying,” recorded Dom German Poirier, erudite Benedictine who was present during the profaning of the tombs. “A foul-smelling, thick, black vapour was released, which they desperately tried to dispel with vinegar and powder that they had taken the precaution of burning.” In 1794, the Arms and Powders Commission had the roof removed in order to get at the strips of lead. The building was in
ruins. A street was very nearly constructed straight through the middle. The vaulted arches were exposed to bad weather, the church served as a storehouse for wheat and flour, there was even talk of destroying the central nave in order to establish a market hall in its place. After the turbulence and torment, the church was finally reinstated as a place of worship.

At the height of his glory, Napoleon decided to have the tomb of his dynasty established in the Basilica of Saint-Denis in order to join the historical continuity of royal families there. Work on a colossal scale was undertaken. A new building-master was named in 1813 but his ignorance of medieval architecture lead to disaster. Although the north spire was rebuilt after falling to the ground as a result of a thunderbolt strike on June 9, 1837, it collapsed under its own weight in 1845. The work was then entrusted to Viollet-le-Duc who continued to masterfully direct the work until 1879. After various excavations revealed pre-existing structures and the existence of Merovingian tombs, the church was elevated to a cathedral in 1966. The Cathedral Basilica of Saint-Denis is divided into two main parts: the nave and lower section are used for Catholic ceremonies, and the transept, choir, ambulatory, and crypt make up the museum. A unique collection in Europe, the museum houses seventy recumbent statues and tombs through which the evolution of funerary art across the centuries can be seen and admired.

**Practical Information**

Cathedral Basilica of Saint-Denis
1, rue de Légion d’Honneur - 93200 Saint Denis
Telephone: +33 (0)1 48 09 83 54.
www.monuments-nationaux.fr

 Métro: Line 13
 Autoroute A1: Exit (Sortie) Saint Denis
 RER: Line D
 Opening Hours: April 1 to September 30: Monday to Friday, 10:00 – 19:00; Sunday, 12 noon – 19:00
 October 1 to March 31: Monday to Friday, 10:00 to 17:00; Sunday, 12 noon – 17:00
 Closures: Jan 1, Nov 1 and 11, Dec 25.

Catholic ceremonies, and the transept, choir, ambulatory, and crypt make up the museum. A unique collection in Europe, the museum houses seventy recumbent statues and tombs through which the evolution of funerary art across the centuries can be seen and admired.

**La Basilique Saint Denis**

Instructions for authors

General instructions

- Manuscripts should be provided by e-mail (udit.siklosi@fr.netgrs.com) or by CD double-spaced, with 2.5-cm margins. Pages must be numbered. Standard typed page = 25 lines of 90 characters (including spaces) double-spaced, 2.5-cm margins = a total of about 320 words per page.
- All texts should be submitted in English.
- Provide 1 color photograph of main author.
- On the title page, provide: a title (concise and informative); full names of authors (first name, middle name initial, and last name); highest academic degrees (in country-of-origin language); affiliations (names of department[s] and institution[s] at the time the work was done); a short running title (no more than 50 letters and spaces); keywords (5-10); corresponding author’s complete mailing address and telephone No., fax No., and e-mail address; acknowledgments (on title page, or at end of main text).
- Include an Abstract of 200-230 words for all texts except Editorials and replies to the Controversial Question.
- Figures and Tables. Figures should be of good quality or professionally prepared, numbered according to their order, with proper orientation indicated (eg, “top,” or “left”). Figures may be provided as pdf files (printing resolution = 300 dpi scans, on CDrom, or via e-mail; screen resolution = 72 dpi scans acceptable only if large-sized format [A4]). Provide fully explicit legends, not repetitive of text. All abbreviations used should be explained in the legends. As figures and graphs may need to be reduced or enlarged, all absolute values and statistics should be provided. Illustrations will be reproduced in full color only when clearly necessary, eg, images from nuclear medicine or histology. Provide each table on a separate sheet, with title above and description below. All figures and tables should be cited in the text, with distinct numbering for figures and tables.
- Note that Editorials and Abstracts will be published in English and French. Translations into French will be provided by the Publisher’s Editorial Department.
- Include Headings using a consistent style for the various levels of headings, to highlight key points and facilitate comprehension of the text. The Editorial Department reserves the right to add or delete headings when necessary.
- Abbreviations should be used sparingly and expanded at first mention. A list of selected abbreviations and acronyms should be provided (or will be prepared by the Editorial Department) where necessary.
- Use Système International (SI) units.
- Use generic names of drugs.
- All references should be cited in the text and numbered consecutively using superscript arabic numerals. Presentation of the references should be based on the Uniform Requirements for Manuscripts Submitted to Biomedical Journals. Ann Intern Med. 1997; 126:36-47 (“Vancouver style”). The author-date system of citation is NOT acceptable. In press references are to be avoided. In the bibliography, titles of journals should be abbreviated according to the Index Medicus. All authors should be listed up to six; if there are more, only the first three should be listed, followed by “et al.”

Where necessary, references will be styled by the Editorial Department to Medicographia copyediting requirements. Authors bear total responsibility for the accuracy and completeness of all references and for correct text citation. Example of style for references:


Specific formats

- Editorial: 1500 words. No abstract or illustrations should be included. A French translation of the Editorial will be provided by the Editorial Department and submitted to the author.
- Theme - Focus - Update - Therapeutic outlook article - Touch of France: Abstract: 200-230 words. Main text: 2800-3200 words. References: their number should not exceed 50. Illustrations (figures and tables): their number should not exceed 5 unless clearly necessary.
- Interview: Abstract: 200-230 words. Main text: 2000-2500 words. Headings are the questions posed at the interview. References, if cited, should in no case exceed 10. No illustrations.
- Replies to the Controversial Question: 400-600 words. No abstract or illustrations should be included. References, if cited, should in no case exceed 6.

Editorial processing

- Editorial style: All contributions to Medicographia will be styled by the Editorial Department according to the specifications of the current edition of the American Medical Association Manual of Style, Williams & Wilkins.
- Page proofs and editorial queries will be sent to the corresponding author for approval. Corrections should be returned within 48 hours by e-mail, and fax or express mail. If this deadline is not met, changes made by the Editorial Department will be assumed to be accepted by the author. Authors are responsible for all statements made in their work, including changes made by the Editorial Department and authorized by the author. Articles and abstracts will be edited to required length or returned to the author if specific requirements are not complied with.

Copyright

- Copyright of articles will be transferred to the Publisher of Medicographia. The Copyright Transfer Agreement must be signed by the main author and all coauthors and returned to the Publisher.
- For reproduction of copyrighted work, it is the author’s responsibility to obtain authorizations from the author(s) (including self) and the publisher(s) and provide copies of these authorizations with the manuscript.