Stable coronary artery disease: an evolving picture

EDITORIAL
3 Stable coronary artery disease in the 21st century: old concepts revisited
La maladie coronaire stable au 21e siècle : évolution des concepts
C. J. Pepine, USA

THEMED ARTICLES
11 Coronary artery disease epidemics: not all the same
C. M. Reid, A. J. Owen, B. Freedman, Australia

19 The evolving clinical patterns of chronic coronary artery disease: clarifying the picture
P. G. Steg, France

25 Impact of stable coronary artery disease on quality of life: the patient’s perspective
M. Tendera, Poland

31 Rethinking the pathophysiology of stable coronary artery disease
A. Huqi, M. Marzilli, Italy

37 Pathophysiology and clinical significance of plaque rupture
G. Niccoli, F. Fracassi, F. Crea, Italy

45 Evolving concepts in defining optimal strategies for the management of patients with stable ischemic heart disease
S. K. Padala, M. S. Sidhu, W. E. Boden, USA

55 Rethinking stent implantation for stable coronary artery disease
W. Wijns, Belgium

63 Heart rate and atherosclerotic plaque rupture: pathophysiological evidence and clinical perspectives
C. Gebhard, E. A. Kritikou, J. C. Tardif, Canada

Contents continued on next page
CONTROVERSIAL QUESTION

73 Should stable CAD patients without angina receive anti-ischemic therapy?
M. Abdel Hamid, Egypt - S. Al-Saif, Saudi Arabia - E. Atalar, Turkey -
L. M. Cesar, Brazil - G. H. Choo, Malaysia - X. Garcia-Moll, Spain -
Y. Karpov, Russia - U. Laufs, Germany - N. Mewton, France -
T. Q. Nguyen, Vietnam - A. N. Parkhomenko, Ukraine - R. Seabra-
Gomes, Portugal - S. Y. Tan, Singapore - C. J. Vaughan, Ireland -
P. H. Zelveian, Armenia

PROCORALAN

89 Clinical benefits of Procoralan (ivabradine): evidence and perspectives
I. Elyubaeva, France

INTERVIEW

98 SIGNIFY: hope for new perspectives in CAD management
K. Fox, United Kingdom

FOCUS

Clinical perspectives in assessment of high-risk atherosclerotic plaques
103 R. Klingenberg, O. Gaemperli, T. F. Lüscher, Switzerland

A TOUCH OF FRANCE

112 Taking Paris by storm: Benjamin Franklin, American Founding Father and first ambassador to France
T. J. Fleming, USA

123 Dr Benjamin Franklin’s scientific and medical legacy
J. V. Hirschmann, USA
Coronary artery disease (CAD) remains a major worldwide threat to health and well-being. Tremendous progress in our understanding of CAD has contributed to a decline in mortality among men and more recently women in the United States and most of Europe. Most progress, however, centers on reduced mortality from acute myocardial infarction (MI). With population aging plus epidemics of obesity and diabetes, there will be increasing numbers with chronic manifestations like stable angina.

This editorial is a summary introduction to stable CAD in the 21st century, the topic of this issue, and will first revisit some terminology concepts. Considerable evidence has countered traditional categorical definition of CAD as presence or absence of flow-limiting stenosis. Revised concepts recognize CAD as a continuous spectrum of disease that is not simply limited to obstructive coronary plaque. Within this spectrum, patients may present with syndromes ranging from totally asymptomatic to highly symptomatic with or without signs of ischemia (ie, insufficient myocardial blood flow). When signs and/or symptoms of ischemia are present, it is appropriate to use the term ischemic heart disease (IHD).

Major changes in the management of stable CAD
Management changes include improved recognition and understanding of demographics and consequences of stable angina and other chronic IHD syndromes like heart failure. The estimated prevalence of stable angina in Western countries is approximately 5% and is increasing, negatively impacting quality of life and ability to work, with considerable economic consequences. Also, there is a substantially higher prevalence of chronic IHD in women.

Stable CAD management traditionally has focused on coronary angiography to identify obstructive lesions and provide direction for revascularization. In the absence of obstructive lesions, patients were told that their symptoms were not cardiac in origin. A milestone in the management of women, and probably men, with signs/symptoms of IHD without obstructive CAD is recognition of the role of coronary microvascular dysfunction. The elderly are another cohort with increased angina prevalence, but an absence of robust data, as with women, defaults such patients to management pathways designed from data collected on younger male cohorts.

In addition, the shift from focusing only on obstructive stenosis has been fueled by failure of revascularization management with percutaneous intervention to uniformly improve outcomes. Coronary bypass surgery decreases mortality and MI rates in se-
Stable CAD in the 21st century – Pepine

Selected abbreviations and acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAD</td>
<td>coronary artery disease</td>
</tr>
<tr>
<td>CFR</td>
<td>coronary flow reserve</td>
</tr>
<tr>
<td>CTA</td>
<td>computed CT coronary angiography</td>
</tr>
<tr>
<td>EPC</td>
<td>endothelial progenitor cell</td>
</tr>
<tr>
<td>FFR</td>
<td>fractional flow reserve</td>
</tr>
<tr>
<td>IHD</td>
<td>ischemic heart disease</td>
</tr>
<tr>
<td>LDL-C</td>
<td>low-density lipoprotein cholesterol</td>
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<tr>
<td>MI</td>
<td>myocardial infarction</td>
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Structure

Coronary angiography data led to the assumption that stable CAD syndromes meant a severe ("flow-limiting") stenosis. New methods evolved to assess stenosis severity: intravascular ultrasound (IVUS), optical coherence tomography (OCT), and coronary computed tomography angiography (CTA) added high-resolution cross-sectional lumen and vessel wall images, including plaque and thrombus if present. These contributions advanced our understanding of lesions associated with MI: the majority result from disruption (rupture/erosion) of nonobstructive plaque.13

Evaluation of stenosis structure remained limited, in part, because blood flow needs of the myocardial segment supplied by the artery were unknown. For coronary segments supplying a large volume of normally functioning myocardium, structural assessment methods may underestimate stenosis severity, while for segments supplying a small volume of functioning myocardium, they tend to overestimate stenosis severity. In clinical practice, reliance of structural metrics alone from angiography evolved to include functional evaluation.14

Function

Stress tests may assess the functional significance of CAD; however, there is wide variability in patient responses even when a flow-limiting stenosis is present.15 Physiologic coronary flow reserve (CFR) evaluation provides an overall functional measure. Stenosis characteristics (cross-sectional area and length) and flow determine the impact of a stenosis on regional perfusion. In practice, fractional flow reserve (FFR) measurement has improved selection of revascularization candidates, but microvascular disease, and/or MI with ischemic left ventricular (LV) dysfunction, may limit the usefulness of FFR assessment.

The coronary microcirculation comprises most of the blood vessels and controls the volume and distribution of myocardial flow, but is not visualized by angiography. It may be indirectly evaluated from speed of contrast flow during coronary angiography as the corrected TIMI (Thrombolysis In Myocardial Infarction) frame count.16 This simple, objective, continuous index is accurate, reproducible, highly correlated with Doppler flow measurements, and provides information for risk

Evolution in understanding the pathophysiologic, cellular, and molecular bases of CAD

Studies of the pathology of coronary artery disease determined that it is caused by atherosclerosis and the associated inflammatory processes, assumed to result from a modern lifestyle. However, evidence of atherosclerosis, in the aorta and major branches including coronary arteries, has been identified in mummies from different preindustrial and hunter-gatherer cultures of over 4000 years ago.12 Smoke exposure and chronic infection likely promoted the inflammation aspects of atherosclerosis. These observations indicate that CAD is more likely a component of human aging that is modulated by diet and lifestyle with genetic, lipid, cellular, and immunologic influences.

Further evolution in understanding of the pathophysiology derives from influences of atherosclerosis on structure and function of the coronary vasculature.

SELECTED ABBREVIATIONS AND ACRONYMS

- **CAD** coronary artery disease
- **CFR** coronary flow reserve
- **CTA** computed CT coronary angiography
- **EPC** endothelial progenitor cell
- **FFR** fractional flow reserve
- **IHD** ischemic heart disease
- **LDL-C** low-density lipoprotein cholesterol
- **MI** myocardial infarction

Selected abbreviations and acronyms

**SPECTRUM OF CORONARY ARTERY DISEASE**

- **NON-OBSTRICTIVE AND OBSTRUCTIVE PLAQUE**
  - **ISCHEMIC HEART DISEASE**
    - Acute coronary syndromes
    - Chronic coronary syndromes

**Figure 1.** The continuous spectrum of coronary artery disease. Coronary artery disease is not simply limited to obstructive coronary plaque. Patients may present with syndromes ranging from totally asymptomatic to highly symptomatic with or without signs of ischemia. Most patients undergoing angiography for symptoms and/or signs of ischemia have nonobstructive plaque. Most acute events are a result of nonobstructive plaque rupture or erosion.

Selected high-risk subgroups (eg, severe ischemia with left main stenosis or multivessel obstruction associated with diabetes), but revascularization in the general stable CAD population has moved to palliation for limiting symptoms persisting with "optimal medical therapy." This now includes, in addition to traditional anti-ischemic agents (nitrates, β-blockers, and calcium antagonists), a late sodium current inhibitor, ranolazine, and an I1-channel inhibitor, ivabradine, plus intense risk factor modification (see below).

Ultrasensitive molecular biomarkers are also impacting management. For example, elevated high-sensitivity cardiac (hs-c) troponin is found in around 40% of stable CAD cases, likely related to micro-rupture/erosion of vulnerable plaques, imparting increased risk for adverse outcomes.10,11
stratification. Studies using gadolinium cardiac magnetic resonance (CMR) in stable post-MI patients support the prognostic value of detecting microvascular obstruction.

Recognition of the prognostic significance of microvascular dysfunction in stable angina and other disorders has fueled interest. The syndrome of microvascular angina without obstructive CAD is highly prevalent, particularly among women with stable angina. The microcirculation can be evaluated, in the absence of flow-limiting stenoses, by CFR or the index of microvascular resistance (IMR).

Functional evaluation of stable CAD patients is also evolving at the cellular and molecular levels. Endothelial progenitor cell (EPC) and smooth muscle cell dysfunction in epicardial and microvessels have been linked with alterations in circulating and bone marrow stem/progenitor cell numbers/functions. Biological differences between EPC populations may be important in vascular function and as indices of epicardial and microvascular disease. EPCs have been implicated in protection against injury and atherogenesis. Given their potential in CV regeneration/repair, exploration of circulating EPCs and other cells as markers of vascular integrity, responses to treatment, and novel therapeutic interventions is under way.

**Evolution in risk factor assessment**

In Western populations, there is a decline in the prevalence of coronary atherosclerosis that is linked with reduction in several risk factors; but these reductions are not uniform across all regions and are far from optimal. Furthermore, aging of Western populations, coincident with epidemics of obesity, dysglycemia, and hypertension worldwide, raise considerable concern for the future. In patients with stable CAD, “optimal medical therapy” now includes modification of risk conditions linked causally with adverse outcomes. These include lifestyle interventions (regular activity, weight loss, heart-healthy diet, smoking cessation) and pharmacotherapy to modify low-density lipoprotein cholesterol (LDL-C), blood pressure, and dysglycemia. Unfortunately, the number of stable CAD patients exposed to structured intervention of major modifiable risk factors remains disappointingly low. Furthermore, only 8%-23% of high-risk patients achieve all goals for LDL-C, systolic blood pressure (SBP), glycated hemoglobin (HbA1c), and smoking.

**Opportunities for further improvement in patient management**

Overall management goals for stable CAD patients focus on improved clinical outcomes and prevention of disease progression and there are many areas where care could be improved. For example, the majority of stable CAD patients have nonobstructive disease, but are currently less likely to receive secondary prevention medications vs patients with obstructive CAD. Additionally, whereas today there is a “one size fits all” approach, more “individualized” or “personalized” management may be possible in the future, guided by evolving biomarkers from genomics, proteomics, and metabolomics. Novel biomarkers are under intensive study and metabolic profiling by nuclear magnetic resonance spectroscopy of peripheral blood promises early detection and quantification of ischemia.

With the well-known limitations of traditional antianginal agents, the development of novel approaches would be useful. Longer-acting derivatives of ranolazine and ivabradine are presently under study and there is also renewed interest in some older drugs (eg, allopurinol, colchicine, trimetazidine) for secondary prevention in stable CAD.

The epidemic of heart failure provides the impetus for finding treatments for prevention of heart failure with preserved ejection fraction (HFpEF) and heart failure with decreased ejection fraction (HFrEF) in chronic CAD patients. The myosin activators in development could theoretically facilitate myocardial contractile work without increasing myocardial oxygen demand, and early studies in stable CAD patients with angina and LV dysfunction are promising.

Some emerging, novel interventions include shock wave therapy, the coronary sinus reducer stent, and myocardial cryotherapy. Cell-based therapy is evolving rapidly for “no revascularization option, refractory angina.” Results with autologous bone marrow–derived CD34+ cells are encouraging, and adipocyte-derived cells, allogeneic mesenchymal cells, and other cell types are under study.

Limiting costs of care is also important. Since the majority of angiograms performed for stable CAD show nonobstructive CAD, a noninvasive measure of FFR would optimize applications and result in cost savings. This has been accomplished with FFR derived from computed tomography (FFRCT), by applying computational fluid dynamics to determine the physiologic significance of CAD to CTA.

There is a substantial need for advances in secondary prevention, as heart failure after MI is a major problem increasingly associated with aging. Microvascular obstruction/dysfunction adds incremental prognostic information, and trials to determine whether stratification based on microvascular dysfunction improves outcomes would be of interest. Treatments targeting the pathologic basis for microvascular injury/dysfunction including ischemia-reperfusion injury and matrix remodeling represent new approaches. Finally, management of patients with angina/other findings of stable CAD without obstructive stenoses represents a challenge for which there is virtually no reliable evidence base. New therapeutic interventions would be of great interest.

These comments, and the following in this issue, reflect the evolution in stable CAD and indicate where future management of this disease is headed.
References


La maladie coronaire stable au 21e siècle : évolution des concepts

par C. J. Pepine, États-Unis

La maladie coronaire (MC) représente toujours une menace majeure pour la santé et le bien-être à l'échelle mondiale. Les immenses progrès accomplis dans la compréhension de cette maladie ont contribué à faire reculer la mortalité chez l'homme et plus récemment chez la femme aux États-Unis1 et dans la plus grande partie de l'Europe2. Toutefois, ces progrès ont principalement concerné la réduction de la mortalité par infarctus aigu du myocarde (IDM)3, ce qui a eu pour conséquence, associé au vieillissement de la population et à l'épidémie d'obésité et de diabète, d'entraîner une multiplication du nombre de patients présentant des manifestations chroniques telles que l'angor stable.

Cet éditorial constitue une brève introduction à la MC stable au 21e siècle, qui est le thème de ce numéro de Medicographia. Il s'attache avant tout à revisiter un certain nombre de concepts liés à cette pathologie et à son traitement, et à montrer comment ceux-ci ont évolué.

Évolution de la définition de la maladie coronaire

De nombreuses données viennent démentir la définition classique qui caractérisait la MC par la présence ou l'absence de sténose réduisant le débit sanguin4. La MC est désormais définie comme un spectre continu dont les composantes pathologiques ne se limitent pas simplement à l'athérome coronarien obstructif (Figure 1, page 8). En effet, ce spectre inclut des syndromes allant de totalement asymptomatiques à hautement symptomatiques, avec ou sans signes et/ou symptômes d'ischémie (secondaires à un débit sanguin myocardique insuffisant). En présence d’ischémie, il convient d’utiliser le terme de cardiopathie ischémique (CI).

Évolution dans la prise en charge de la maladie coronaire stable

La prise en charge de la MC stable a notamment évolué à travers une meilleure reconnaissance et compréhension des caractéristiques démographiques et des conséquences de l’angor stable et des autres syndromes de CI chroniques, comme l’insuffisance cardiaque. La prévalence estimée de l’angor stable dans les pays occidentaux est d’environ 5 % et ne cesse d’augmenter13, ce qui a un impact négatif sur la qualité de vie et l’aptitude au travail, avec les conséquences économiques désastreuses que cela comporte. On note également une prévalence de CI chronique nettement plus élevée chez la femme4,6,7.

La prise en charge de la MC stable reposait traditionnellement sur la coronarographie, utilisée pour identifier d’éventuelles lésions obstructives et guider la revascularisation. Lorsque de telles lésions étaient absentes, on affirmait aux patients que
Les symptômes n’étaient pas d’origine cardiaque. La reconnaissance du rôle du dysfonctionnement microvasculaire coronarien a marqué un tournant dans la prise en charge des coronariens chroniques.

Les personnes âgées constituent une autre cohorte présentant une prévalence accrue d’angor. Cependant, en l’absence de données solides les concernant (comme c’est également le cas pour les femmes), ces patients sont orientés par défaut vers des traitements établis sur la base de données obtenues dans des cohortes d’hommes plus jeunes.

En outre, l’approche consistant à se focaliser uniquement sur les sténoses obstructives a été abandonnée, notamment suite à l’échec de la revascularisation par intervention coronaire percutanée à réduire les manifestations de manière uniforme. Le pontage aorto-coronarien contribue à faire baisser les taux d’IDM et de mortalité dans les sous-groupes sélectionnés présentant un risque élevé (par ex., ischémie sévère avec sténose du tronc coronaire gauche ou obstructions multivasculaires associées au diabète), mais la revascularisation de la population générale présentant une MC stable est devenue un pari allant visant à limiter les symptômes persistants, ce qui augmente le risque d’évolutions défavorables.

Évolution dans la compréhension des bases physiopathologiques, cellulaires et moléculaires de la maladie coronaire

Des études anatomopathologiques portant sur la MC ont permis de déterminer que l’athérosclérose et les processus inflammatoires associés, supposés résulter de notre mode de vie moderne (en particulier le tabagisme), étaient à l’origine de cette maladie. Cependant, la présence d’athérosclérose au niveau de l’aorte et ses principales branches, dont les artères coronaires, a été mise en évidence chez des momies issues de diverses cultures préindustrielles et de chasseurs-cueilleurs datant de plus de 4 000 ans. L’exposition aux infections chroniques favorise probablement aussi les aspects inflammatoires de l’athérosclérose. Ces observations indiquent que la MC est vraisemblablement une composante du vieillissement humain qui est modulée par l’alimentation et le mode de vie, et soumise à diverses influences génétiques, lipidiques, cellulaires et immunologiques.

Les avancées dans la compréhension des effets de l’athérosclérose sur la structure et la fonction des vaisseaux coronariens permettent désormais de mieux cerner la physiopathologie de la MC.

Structure

Les données fournies par la coronarographie ont conduit à l’hypothèse selon laquelle les syndromes de MC stable résultent d’une sténose entraînant une « limitation sévère du débit sanguin ». De nouvelles méthodes ont été développées permettant d’évaluer la gravité de la sténose : ainsi, l’échographie intravasculaire (IVUS), la tomographie par cohérence optique (TCO) et l’angiographie coronaire par tomodensitométrie (TDM coronaire) donnent des images haute résolution de coupes transversales de la paroi et de la lumière vasculaires, et, le cas échéant, de la plaque et du thrombus. Ceci a permis de comprendre que les lésions associées à l’IDM résultent pour la plupart d’altérations (rupture/érosion) touchant des plaques non obstructives.

L’évaluation de la structure de la sténose demeurait limitée, en partie, car les besoins en flux sanguin de la région myocardique irriguée par l’artère, étaient inconnus. Pour les segments coronaires irriguant un volume important de myocarde fonctionnant normalement, les méthodes d’évaluation de la structure peuvent sous-estimer la gravité de la sténose, alors que lorsqu’il s’agit d’un petit volume, la gravité de la sténose est souvent surestimée. C’est pourquoi l’évaluation fondée uniquement sur des mesures structurelles par angiographie a évolué afin d’inclure une évaluation fonctionnelle.

La maladie coronaire stable au 21e siècle – Pepine


Évolution de l’évaluation des facteurs de risque
Dans les populations occidentales, on assiste à une diminution de la prévalence de l’athéroscorose coronarienne, en rapport avec une réduction de plusieurs facteurs de risque⁶. Cependant, ces réductions ne sont pas uniformes dans toutes les régions et sont loin d’être optimales. Par ailleurs, le vieillissement des populations occidentales, parallèlement aux épidémies mondiales actuelles d’obésité, de troubles de l’équilibre glycémique et d’hypertension, soulève de sérieuses craintes pour l’avenir.

Chez les patients présentant une MC stable, le « traitement médical optimal » englobe désormais une modification des conditions de risque présentant une relation de causalité avec une évolution défavorable. Ceci inclut des interventions sur le mode de vie (activité régulière, perte de poids, alimentation saine pour le cœur, sevrage tabagique) et le traitement médicamenteux du cholestérol associé aux lipoprotéines de basse densité (C-LDL), de la tension artérielle et des troubles de l’équilibre glycémique. Malheureusement, le nombre de patients ayant une MC stable bénéficiant d’une intervention structurée sur les principaux facteurs de risque modifiables demeure faible et décevant. Par ailleurs, 8 à 23 % seulement des patients présentant un risque élevé atteignent les objectifs concernant le C-LDL, la tension artérielle systolique, l’hémoglobine glyquée (HbA₁c) et le tabagisme⁶⁸.

Conclusion : perspectives d’amélioration de la prise en charge des patients
magnétique nucléaire du sang périphérique laisse apparaître l’espoir d’une détection précoce et d’une quantification de l’ischémie\(^3\)\(^0\).

Étant donné les limites bien connues des antiangineux classiques, le développement de nouvelles approches serait utile. Des dérivés à action prolongée de la ranolazine et de l’ivabradine sont actuellement à l’étude, et on assiste également à un regain d’intérêt pour certains anciens médicaments (par exemple, l’allopurinol, la colchicine, la trimétazidine) dans la prévention secondaire de la MC stable\(^3\)\(^1\)-\(^3\)\(^3\).

L’épidémie d’insuffisance cardiaque stimule la découverte de traitements pour la prévention de l’insuffisance cardiaque à fraction d’éjection préservée (ICFEP) et de l’insuffisance cardiaque à fraction d’éjection diminuée (ICFED) chez les patients présentant une MC chronique. Les activateurs de la myosine en développement pourraient en théorie faciliter la contractilité myocardique sans augmenter la demande myocardique en oxygène, et les premières études menées sur les patients présentant une MC stable avec un angor et un dysfonctionnement ventriculaire gauche sont prometteuses. Parmi les interventions émergentes figurent le traitement par ondes de choc\(^3\)\(^4\), le stent réducteur de sinus coronaire\(^3\)\(^5\) et la cryothérapie myocardique\(^3\)\(^6\).

La thérapie cellulaire connaît un essor rapide dans le cadre de « l’angor réfractaire non revascularisable ». Les résultats obtenus avec des cellules CD34\(^+\) autologues dérivées de la moelle osseuse sont encourageants\(^3\)\(^7\), et les cellules dérivées des adipocytes, les cellules mésenchymateuses allogéniques et les autres types de cellules sont à l’étude.

Il est également primordial de limiter les coûts des traitements. Étant donné que la majorité des angiographies réalisées chez les patients présentant une MC stable révèlent une forme non obstructive\(^3\)\(^8\)-\(^3\)\(^9\), la mesure non invasive de la FFR permettrait d’optimiser les applications et de réaliser des économies. C’est ce que permet déjà le calcul de la FFR par tomodensitométrie (FFR-TDM), en utilisant les principes quantitatifs de la dynamique des fluides pour déterminer l’importance physiologique de la MC\(^4\)\(^0\)-\(^4\)\(^1\).

Il est impératif de réaliser des progrès dans la prévention secondaire, l’insuffisance cardiaque post-IDM étant un problème majeur de plus en plus associé au vieillissement. L’obstruction et le dysfonctionnement microvasculaires fournissent des informations pronostiques supplémentaires, et des études pour déterminer si la stratification basée sur le dysfonctionnement microvasculaire améliore les résultats seraient très utiles. Les traitements ciblant les processus physiopathologiques des lésions et du dysfonctionnement microvasculaires, comme l’ischémie-reperfusion et le remodelage de la matrice extracellulaire, constituent de nouvelles approches.

Enfin, la prise en charge des patients présentant un angor ou d’autres signes de MC stable sans sténoses obstructives représente un défi pour lequel il n’existe pratiquement aucune base factuelle fiable. De nouvelles interventions thérapeutiques revêtiraient un grand intérêt.

Les points évoqués dans cet éditorial et les autres articles de ce numéro font le point sur la situation actuelle de la MC stable et les perspectives qui se dessinent pour sa prise en charge à l’avenir.
Rapid economic development in low- and middle-income developing economies combined with global aging are 2 major contributors to a potential second-wave epidemic, which will ensure that cardiovascular disease (CVD) remains the number one cause of death and disability around the globe over the foreseeable future. Much has been learned in the second half of the 20th century on underlying risk factors and strategies for cardiovascular disease prevention that may assist countries in Asia, Africa, the Middle East, and Eastern Europe in developing their own effective prevention and management strategies, although a great deal of the problem is economic and related to relative poverty. The reduction seen in CVD death rates in many Western high-income economies over the past decades demonstrates that with effective implementation, much can be done to reduce the individual and community burden. However, major challenges remain in terms of supporting and maintaining a population-based approach by promoting lifestyle-related strategies through public policy and community development, while at the same time effectively allocating limited health care resources to access modern advances in cardiovascular treatments and management at the individual level. Furthermore, there may well be differences in the background risk and presentation of coronary artery disease in this second-wave epidemic due to the accelerated changes in lifestyle and economic development associated with this epidemiological transition occurring in many parts of the world previously having limited exposure to lifestyle-related chronic disease.

Coronary artery disease (CAD) has been consistently ranked as the number one cause of death and disability in most Western industrialized countries since the mid-1950s. Since reaching a peak in the 1960s and early 1970s, CAD rates have declined considerably, yet CAD remains a major cause of much of the disease burden in these countries. In addition, we are now seeing a second-wave epidemic in low-to-middle-income countries where previously communicable disease was the primary cause of mortality in the community. This article will examine the underlying features of these CAD epidemics and identify the major issues that need to be addressed across the globe in order to reduce the impact, from the individual, community, and societal perspectives.

A world in rapid transition
There are striking differences in the prevalence of CAD, as different regions of the world face different stages of the epidemic. The epidemiologic transition model for car-
Coronary artery disease epidemics: not all the same – Reid and others

Stable coronary artery disease: an evolving picture

Diovascular diseases (CVDs) (Table I) describes a series of stages starting from a population profile with a low life expectancy and CVD arising mostly from infectious disease and malnutrition, a pattern commonly seen in low-income/less-developed countries. As economic and public health development improves population nutrition and reduces infectious disease, life expectancy increases and both the pattern and rates of CVD change. In stage 4, commonly seen in high-income countries, life expectancy increases and degenerative CVDs in older age predominate. The varying incidence, prevalence, and mortality rates reflect the different levels of risk factors, other competing causes of death, and availability of resources to combat CVD.

Historically, the transition from stage 1 through to stage 4 has taken hundreds to thousands of years, but the 20th century has seen an unprecedented rate of development in historically low-income developing countries. Economic globalization has been a fueling factor and the economic development of many low-income developing nations has resulted in a rapid rise in CAD burden due to socioeconomic changes, increase in lifespan, and acquisition of lifestyle-related coronary heart disease risk factors.

Global aging

Despite a perception that population aging is an issue only for high-income, well-developed countries, the majority of the world’s population over the age of 60 live in developing nations (Figure 1). Between 2000 and 2050, the proportion of the world’s population aged over 60 years will double from around 11% to 22%. The absolute number of people aged 60 years and over is expected to increase from 605 million to 2 billion over the same period. The rate of increase in developing countries is unprecedented. For example, it took more than 100 years for the share of France’s population aged 65 or older to double from 7% to 14%. In contrast, it will take countries like Brazil and China less than 25 years to reach the same growth. Given the increasing risk of CVD with increasing age, even in poor countries, most older people die of diseases such as heart disease, cancer, and diabetes rather than from infectious and parasitic diseases. In addition, older people often have several health problems at the same time, such as diabetes and heart disease.

First-wave cardiovascular epidemic

Following the end of the Second World War in 1945, CAD was relatively stable in the United States, with the age-adjusted death rates accounting for 439 deaths per 100 000 people. This figure remained relatively stable until the 1950s when disease rates began to rise and peaked in 1969 at a rate of 470 deaths/100 000 in the population. Approximately 58% of all deaths in the United States in 1968 were of cardiovascular cause, with 37% being due to CAD. Rates of this magnitude

<table>
<thead>
<tr>
<th>Stages of development</th>
<th>Life expectancy</th>
<th>Deaths from CVD (% of total deaths)</th>
<th>Predominant CVDs and risk factors</th>
</tr>
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<tbody>
<tr>
<td>Stage 1</td>
<td>35 years</td>
<td>5-10</td>
<td>Rheumatic heart disease, infections, and nutritional cardiomyopathies</td>
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<tr>
<td>Stage 2</td>
<td>50 years</td>
<td>10-35</td>
<td>As above + hypertensive heart disease and hemorrhagic strokes</td>
</tr>
<tr>
<td>Stage 3</td>
<td>&gt;60 years</td>
<td>35-65</td>
<td>All forms of strokes, ischemic heart disease at young ages, increasing obesity, and diabetes</td>
</tr>
<tr>
<td>Stage 4</td>
<td>&gt;70 years</td>
<td>&lt;50</td>
<td>Stroke and ischemic heart disease at old age</td>
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</table>

Figure 1. The changing structure of the world’s population.

The world’s population in aging and, in developed countries, the size of the elderly population has already surpassed that of the 12-24-year age group.

were observed in other Western industrialized countries such as Finland, Australia, and the United Kingdom. A number of cross-sectional epidemiological cohort and longitudinal studies identified key clinical and lifestyle-related risk factors such as cigarette smoking, blood cholesterol levels, age, and blood pressure (BP) to be major drivers of risk and further research continued to improve our understanding of the social determinants of CAD risk.

**Landmark studies of cardiovascular risk**

The Framingham Heart Study, commencing in the 1950s has been one of the key observational studies that has enabled a better understanding of the underlying factors associated with increasing risk of CVD. Another important early study of CAD risk factors was the Seven Countries Study, which provided insight into the importance of plasma cholesterol on CAD risk and the influence of cultural and lifestyle factors. Studies such as Framingham and the Seven Countries Study provided the impetus for development of the World Health Organization (WHO) MONICA (Multinational MONItoring of trends and determinants in CArdiovascular disease) Project, which made an important contribution to international standardization of cardiovascular mortality, morbidity, and risk-factor measurement. Coronary disease in individuals and in populations is significantly related to levels of BP, blood lipoproteins, cigarette smoking, age, family history, diabetes mellitus, obesity, and physical inactivity.

**Strategies for prevention**

Understanding the underlying risk factors for CAD paved the way for the development of strategies for disease prevention, which could broadly be divided into 2 approaches: (i) a high-risk approach involving identification of those most at risk through medical assessment and risk-factor screening and (ii) a population strategy to encourage shifts in the level of risk factors in the population at large. Three key factors emphasized the need for a population-based approach to CAD prevention. Firstly, in two-thirds of cases during this epidemic, the initial manifestation of coronary disease was sudden death and acute myocardial infarction (MI), and over half of all heart attack deaths occurred before the victims reached hospital. Although some individuals are in a position to benefit from the advances in emergency hospital care and antithrombotic and antiarrhythmic therapy, the high proportion in whom the catastrophic cardiovascular event occurs without prior warning highlights the importance of population risk-factor reduction as a prevention strategy for sudden cardiac death or MI. This population-based approach is critical both for primary and secondary prevention of CAD. Half of the coronary deaths and MIs will occur in people with known CAD, underscoring the parallel importance of secondary prevention to reduce premature death and MI.

Premature mortality attributed to CAD imposes a high social and economic burden on society, and there is evidence to suggest that environmental, social, and behavioral determinants may be a greater contributor to risk than genetic risk factors. This has been well demonstrated in studies of migrant populations who tend to adopt the dietary and lifestyle patterns of their new home and also demonstrate the increased risk factors and mortality rates of their new homeland.

**Turning the tide**

The continued monitoring and reporting of CAD mortality has demonstrated the remarkable effect of disease prevention strategies over the past 30 years on these initial high rates. Figure 2 illustrates the percentage change in age-adjusted mortality rates from 1950 to 2008 in the United States. Based on data from reference 3: National Heart, Lung, and Blood Institute. Morbidity and mortality: 2012 Chart Book on Cardiovascular, Lung, and Blood Diseases. Washington DC: National Institutes of Health; 2012.

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**Selected abbreviations and acronyms**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>ACE</td>
<td>angiotensin-converting enzyme</td>
</tr>
<tr>
<td>BMI</td>
<td>body mass index</td>
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<tr>
<td>BP</td>
<td>blood pressure</td>
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<tr>
<td>CAD</td>
<td>coronary artery disease</td>
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<tr>
<td>CVD</td>
<td>cardiovascular disease</td>
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<tr>
<td>MI</td>
<td>myocardial infarction</td>
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<tr>
<td>MONICA</td>
<td>Multinational MONItoring of trends and determinants in CArdiovascular disease</td>
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<tr>
<td>OECD</td>
<td>Organization for Economic Cooperation and Development</td>
</tr>
<tr>
<td>STEPS</td>
<td>STEPwise approach to Surveillance</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
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While the administrative morbidity and mortality statistics provide the key information on outcomes, they do not provide information on the factors underlying these changes observed over time. Clearly, advances in medical care, including the introduction of mobile intensive care ambulances, the widespread use of lipid-lowering and BP-lowering drugs, the introduction of medical devices, including drug-eluting and bare-metal intracoronary stents, as well as surgical procedures have undoubtedly had a major impact.

Public health policy in Australia has led the world in relation to cigarette smoking, and has had a major impact as community-wide smoking rates have declined over the past decades in most age groups.

These health-promotion and health system–wide changes have most likely contributed to the shift in the prevalence of the well-known risk factors for incident cardiovascular events—smoking, BP, and elevated cholesterol. For example, gains made in reducing the burden of CAD in developed countries are well illustrated by the North Karelia Project. Rates of heart disease mortality in Finland in the late 1960s were among the highest in the world. In 1972, a community-based preventive health program was implemented in the North Karelia region aiming to reduce risk factors for CAD. Over the next 35 years, total cholesterol was reduced by 1.5 mmol/L, diastolic BP was reduced by 8.7 mm Hg, and smoking prevalence was reduced by 15 percentage points. These changes were accompanied by an 80% reduction in CAD mortality in middle-aged men, and it was estimated that three-quarters of the risk reduction could be attributed to improvements in these key risk factors. The halving of CVD seen in a number of developed/high-income countries over the past 3 decades has been accompanied by significant developments in pharmaceuticals, clinical guidelines, devices, and surgical intervention for secondary prevention of CAD. However, 50%-75% of the fall in CAD mortality is attributed to population-wide improvements in major risk factors such as smoking, BP, and cholesterol (largely primary prevention), while secondary prevention strategies (including aspirin, thrombolysis, angiotensin-converting enzyme [ACE] inhibitors, statins, coronary artery bypass surgery) explain the remaining 25%-50% of the reduction in mortality.

Second-wave epidemic

Eastern Europe, Africa, the Middle East, and Asia are the key focal points for the second wave of the CVD epidemic sweeping across the globe (Figure 3). From a positive perspective, much of what has been learned from the first-wave epidemic in regard to the underlying risk factors and population strategies for prevention may well be adapted to suit local countries. However, in many developing low-income countries, information systems are lacking on the prevalence and treatment of cardiovascular risk factors in the community. The WHO has developed a risk assessment program (STEPS [STEPwise approach to Surveillance]) that has been adapted and modified to local conditions in order to gain information on the current state of CVD risk factors in these regions. Mortality statistics and cause of death in particular are also more difficult to quantify in most developing countries, particularly in rural and remote areas around the Asian region. What we can be sure about, however, is that CVD is currently and will continue to be the major cause of death and illness in these developing countries for the foreseeable future.
◆ Are all epidemics the same?

The data collected from developing countries support the role of those key underlying risk factors identified during the first wave of the CAD epidemic, and suggest that they remain important targets for prevention in developing countries.27-30 International CVD procedural and management registries are also providing important information on the characteristics of patients presenting for CVD management in developing countries.31 The REACH Registry (REduction of Atherothrombosis for Continued Health) was an observational prospective cohort study of over 67,000 patients from 44 countries around the world, including many economically developing countries in Asia, the Middle East, and Eastern Europe. These data highlighted that across all countries, classic cardiovascular risk factors are consistent and common in patients with coronary disease and are largely undertreated and uncontrolled.31 Most importantly, one-year cardiovascular event rates were highest in Eastern Europe, the Middle East, and Asian countries (with the exception of Japan) with the cardiovascular death rate being almost double that observed in Australia.32 The difference in one-year rates may be related to differences in medical management and risk-factor profiles across the regions.

The extent and prevalence of diabetes as a comorbidity in addition to smoking, hypertension, and hyperlipidemia may be of particular relevance to populations facing increases in rates of CVDs. In studies on Malays, Indians, and Chinese undergoing percutaneous coronary intervention in Singapore, diabetes rates were 44%, 48%, and 33%, respectively. This is considerably different to the 24% rate observed in an Australian cohort of patients undergoing similar procedures.33 More importantly, strong ethnic differences in MI event, case-fatality, and coronary mortality rates have been observed among the 3 ethnic groups in Singapore. While Indians had the greatest MI event rates, Malays had the highest case-fatality rates.34 Compared with the Chinese, MI event rates were >2 and >3 times higher, and age-standardized coronary mortality rates were 2.4 and 3.0 times higher for Malays and Indians, respectively. Malays had the highest 3.1-year case-fatality rates, with an adjusted hazard ratio of 1.26 (95% confidence interval, 1.14 to 1.38) compared with the Chinese.34

It is possible that some genetic factors may predispose or protect against acute CAD events. Previous studies have reported that Indians present a varied cardiovascular risk profile, characterized by a high prevalence of insulin resistance, glucose intolerance, central obesity, and diabetes, along with other CAD risk indicators, including the plasminogen activator inhibitor-1, homocysteine, and lipoprotein(a).35 Evidence that this risk pattern is related to genetically determined ethnic factors and that it is directly responsible for the higher risk of CAD events in this ethnic group is lacking. Although it is very likely that ethnic variations in the incidence and, possibly, clinical outcome of acute CAD events exist, the causes for such differences are many and difficult to address fully, given the complex interplay of contributing factors, and at least in the INTERHEART (not an acronym) study, the risk factors associated with MI differed little between many different ethnic groupings and explained most of the variance in MI rate.30,35

CAD prevention strategies

At a population level, the key risk factors for CAD are those shared by most noncommunicable diseases; namely, tobacco use, an unhealthy diet, physical inactivity, and harmful alcohol consumption. For effective CAD prevention, not only are long-term strategies for prevention and reduction of risk factors required, but also ongoing surveillance and monitoring, and provision of early detection and treatment in primary care settings. In many developing/low-to-middle-income countries, hospital-based care dominates national health budgets and a large proportion of people with high cardiovascular risk remain undiagnosed, or may have insufficient access to effective preventive treatment at the primary care level.

Key priorities include provision of the following in primary care/low-resource health settings: cardiovascular risk assessment and management for prevention of CAD, diabetes management to prevent secondary complications, smoking cessation programs, and equitable access to essential preventive medicines (aspirin, antihypertensive and lipid-lowering drugs, insulin). Similar approaches are also required in secondary prevention. This needs to be supported by public health, regulatory, and educational frameworks to promote reduced tobacco smoking, consumption of a healthy diet, reduced alcohol consumption, and reduced sedentary behavior.

In modeling undertaken to look at the potential impact of key CAD prevention strategies in a high-income–country setting (eg, US population), smoking cessation was the most cost-effective intervention for reducing the burden of CAD and was the only strategy for which the savings achieved through reductions in cardiovascular events offset the costs of implementation.36 WHO recommendations for addressing tobacco use include development of national infrastructure for tobacco control (government units, either stand-alone or within health ministries) that is protected from commercial or other vested interests of the tobacco industry; price and tax measures to reduce tobacco consumption; protection from tobacco smoke in enclosed spaces; packaging and labeling of tobacco products; bans on tobacco advertising and sponsorship; educational public health campaigns; and accessible smoking cessation programs.

At a population level, regulatory and educational campaigns to reduce dietary salt and trans-fat intake and price and tax measures to reduce alcohol consumption have also been put forward as strategies to combat CAD risk factors. Elimination/reduction of industrially produced trans-fats in the US food supply (by use of alternatives to partially hydrogenated oils in cooking), is thought to have the potential to reduce MI and CAD mortality by more than 6%.37
Obesity and physical inactivity are closely related, and are
associated with increased risk of developing hypertension, dys-
lipidemia, and insulin resistance. Interestingly, the CAD risk of
those with a high body mass index (BMI) who are physically
active/fit appears to be equal to, if not lower than, those with
a normal BMI who are physically inactive/unfit, suggesting
that physical inactivity (and its cardiometabolic sequelae) is a
significant contributor to risk. Data from the US Aerobics Cen-
ter Longitudinal Study suggested that in overweight or obese
men, the risk increase for cardiovascular mortality associated
with low fitness was of a similar magnitude to the risks imposed
by hypertension or high cholesterol levels. However, com-
pliance with physical activity prescriptions or recommenda-
tions is generally very poor: for every 17 sedentary adults re-
ferred by a doctor to a formalized exercise scheme, only 1
would be likely to become moderately active.42 The relatively
higher compliance rates and lower costs of BP- and lipid-low-
ering medications make them an important strategy for risk
reduction.

However, the long-term use of recommended preventive car-
diovascular drug therapy is inadequate among people at high
risk of CVD and this is particularly the case in low- and middle-
income countries. Treatment and adherence gaps are also
described in relatively wealthy Organization for Economic Co-
operation and Development (OECD) countries with highly de-
veloped health care infrastructure and resources.43 In Australia,
recent audits of primary health care practices have indicated
that combination prescription rates of guideline-indicat-
ed BP-lowering drugs, statins, and antiplatelet agents are as low as
50%44,45 and poor compliance results in lower overall use of
these drugs.45

The reasons for low levels of long-term use of preventive med-
ications are multiple and complex.46 Barriers to doctors adopt-
ing guideline recommendations can include lack of time, a
confusing multiplicity of guidelines, lack of awareness of guide-
lines, and insufficient resources to implement the recommenda-
tions.45-61 Low levels of use of prescribed medications can
be associated with taking multiple medicines with complex
dosing regimens, inadequate knowledge about such med-

A strategy based on the use of fixed-dose combination ther-
apy (cardiovascular “polypills”) with generic drug components
may help reduce these treatment gaps by reducing cost and
complexity of drug regimens and by therapeutic inertia. This
may well be a key target for prevention, as Yusuf hypothesized
that a polypill combination (aspirin, a β-blocker, a statin, and
an ACE inhibitor) could reduce CVD events by 75% in those
with vascular disease. Similarly, Wald and Law have proposed
that a polypill containing 3 BP-lowering drugs from different
classes— aspirin, a statin, and folic acid, each at half doses—
for all individuals with established CVD and all those older than
55 years without CVD would safely reduce ischemic heart dis-
ease events by 88% and strokes by 80%.57,58

Studies are currently under way around the world in low-in-
come developing countries and high-income countries to test
whether this approach will have a significant impact on the
second wave of the CVD epidemic across the globe.

Future challenges
Some projections have suggested that gains in reducing the
burden of CAD and increasing life expectancy in developed
countries over the past few decades may begin to be reversed
by the increasing prevalence of obesity and diabetes brought
about by unhealthy diets and increasingly sedentary lifestyles.58
As changes to work and technology continue to reduce in-
cidental or occupational physical activity, development of pub-
lic health strategies to combat physical inactivity presents a
major challenge.

CAD also disproportionately affects those in lower socioeco-
nomic groups. A vicious cycle can be created whereby poverty
exposes people to behavioral risk factors for CAD, and the
onset of disabling or fatal CAD in primary breadwinners can
lead families into further poverty. Ensuring timely and afford-
able access to effective primary prevention remains a chal-
lenge in many countries around the globe.

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Keywords: aging; cardiovascular epidemic; coronary artery disease; economic development; lifestyle; population risk-factor reduction; prevention strategies
MALADIE CORONAIRe : VERS UNE SECONDE VAGUE ÉPIDÉMIQUE

Le développement économique rapide des pays émergents à revenu faible et intermédiaire ainsi que le vieillissement de la population mondiale constituent deux facteurs qui contribuent de façon majeure à une seconde vague épidémique potentielle qui assurera à la maladie cardio-vasculaire (MCV) de demeurer la première cause de décès et d’invalidité dans le monde dans un avenir prévisible. La seconde moitié du XXᵉ siècle a été riche d’enseignement sur les facteurs de risque et les stratégies de prévention de la MCV. L’Asie, l’Afrique, le Moyen Orient et l’Europe de l’Est pourraient s’en inspirer pour développer leurs propres techniques efficaces de prévention et de prise en charge, bien que le principal problème soit d’ordre économique et fonction du degré de pauvreté relative de ces pays. Ces dernières décennies, la réduction des décès par MCV observée dans les pays occidentaux à revenu élevé montre qu’une mise en place efficace peut diminuer l’impact économique des coûts de santé individuels et collectifs de façon importante. Les principales difficultés résident néanmoins dans la mise en place et le maintien d’une approche basée sur la population : il s’agit d’encourager des stratégies axées sur le mode de vie par une politique publique et le développement au niveau local, tout en attribuant efficacement des ressources de soins limitées pour permettre l’accès aux avancées modernes des traitements cardio-vasculaires et de la prise en charge individuelle. Par ailleurs, la seconde vague épidémique évoquée peut comporter des différences dans le risque de fond et le tableau clinique de la MCV en raison des changements accélérés du mode de vie et du développement économique liés à l’apparition de cette transition épidémiologique dans de nombreux endroits ayant été peu exposés autrefois aux maladies chroniques liées au mode de vie.
Despite major advances in the prevention and acute management of coronary artery disease (CAD), the condition remains the number one cause of death worldwide. The presentation and management of patients with chronic CAD has changed drastically over the past decades. In the past, management of such patients largely involved measurement and control of anginal symptoms, with careful dosing of one or more antianginal agents. Over the years, however, the emergence of myocardial revascularization, improved secondary prevention measures, and the availability of novel potent antianginal agents have dramatically changed the clinical presentation of chronic CAD such that patients are now largely asymptomatic, with angina or ischemia rarely present; moreover, if angina or ischemia are identified, they often lead to delineation of the coronary anatomy by angiography with a view to revascularization. Yet, the clinical benefit of routine revascularization in patients with stable CAD is at best uncertain. The ongoing ISCHEMIA study (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) will determine the benefit of anatomical assessment of these patients compared with routine medical therapy alone. In the interim, the ongoing international observational registry CLARIFY (prospective observational Longitudinal Registry of patients with stable coronary artery disease), which was started in 2009-2010 in 46 countries, aims to collect contemporary information on the clinical characteristics, management, and outcomes (over a period of up to 5 years) of a large cohort (approximately 33 000 patients) representing a broad spectrum of stable outpatients with CAD. An ongoing analysis will describe the relative prevalence and prognostic impact of both anginal symptoms and the presence or absence of myocardial ischemia on noninvasive testing.

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Changing epidemiology of coronary artery disease

There have been spectacular advances in the management of patients with coronary artery disease (CAD) over the past 3 decades, particularly in the field of acute coronary syndromes (ACS). The advent of effective reperfusion therapy, first with thrombolysis and subsequently with primary percutaneous coronary intervention (PCI), has been accompanied by steady progress in adjunctive antithrombotic therapy combining effective anticoagulant and antiplatelet therapy. There has also been progress in secondary prevention, with standardized management including liberal use of β-blockers, statins, angiotensin-converting enzyme in-

The evolving clinical patterns of chronic coronary artery disease: clarifying the picture

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hibitors, and long-term antiplatelet therapy. Together, all of the aforementioned therapies have resulted in spectacular reductions in the lethality and complications of ACS. These reductions have been consistently documented in international registries, such as GRACE (the Global Registry of Acute Coronary Events),1 and national registries, such as SWEDEHEART/RIKS-HIA ([Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies]/[Register of Information and Knowledge about Swedish Heart Intensive care Admissions]) in Sweden, the French acute myocardial infarction (AMI) registries, and the Danish registry in Denmark (Figure 1).2-4

In parallel with advances in the management of ACS, progress in prevention of cardiovascular events has also resulted in a reduction in the incidence of AMI and a decrease in deaths from coronary heart disease, at least in the "Western world."5 Detailed analyses and modeling of such reductions have consistently shown that the bulk of these reductions is attributable to risk factor modifications, rather than acute treatment.5 However, despite this encouraging news, the epidemiology of CAD also shows worrisome signals: first, CAD is no longer solely a “disease of the West.” In fact, data show that the global burden of CAD has shifted to low- and middle-income countries, which account for the vast majority of cardiovascular deaths worldwide.6 For example, CAD mortality rates are much higher in Turkmenistan than in Western Europe or North America.7 This is related to the epidemiological transition that is occurring in many of the low- and middle-income countries, and to their large weighting in terms of the overall world population. This explains why, despite all of the progress that has been made, CAD remained the leading cause of death worldwide in 2010, ahead of stroke and chronic obstructive pulmonary disease.8,9 There are other worrying signals beyond the mortality data: the proportion of younger women among patients hospitalized for AMI is increasing, which parallels the increase in smoking prevalence among younger women and the increasing prevalence of obesity in the young.3,5

The emergence of revascularization

Another major change in the management of CAD has been the emergence of revascularization, particularly PCI, as a “dominant” modality for treatment. This stems from the documented mortality benefit of primary PCI for ST-segment elevation AMI,10,11 but also from the established clinical benefits of PCI in moderate-to-high-risk ACS.12-14 With the clear demonstration of these benefits, many countries and hospitals have worked to establish solid PCI centers that are able to provide round-the-clock access to effective PCI. Obvious-
ly, the availability of PCI for ACS opens the door to performing routine PCI for stable CAD. Paradoxically, however, at the same time as PCI has emerged as the standard of care for management of most patients with ACS, data regarding the use of PCI for stable CAD have failed to demonstrate a clear benefit in terms of clinical outcomes.\textsuperscript{15,16} Randomized trials performed in the 20th century that compared PCI with conservative medical therapy did not show a reduction in death or in the composite end point of cardiac death and myocardial infarction (MI).\textsuperscript{17} Later, the COURAGE trial (Clinical Outcomes Utilizing Revascularization and Aggressive druG Evaluation) compared optimal medical therapy (OMT) alone with OMT plus PCI. While approximately one-third of patients who were initially managed with medical therapy ultimately required intervention, there was no difference between the 2 study arms in clinical outcomes over 5 years.\textsuperscript{18} The only benefit of routine early PCI was a modest, but significant, reduction in anginal symptoms; however, this did not remain significant after 3 years.\textsuperscript{19}

The results of COURAGE were subsequently confirmed by the BARI 2D trial (Bypass Angioplasty Revascularization Investigation 2 Diabetes), which was performed in 2368 patients with diabetes and stable CAD (of whom 82\% were symptomatic with angina) and compared revascularization with medical therapy.\textsuperscript{20} Again, after 5 years of follow-up, there was no difference between the study arms in terms of survival, or survival without major adverse cardiovascular events. Thus, overall, routine PCI has not demonstrated any clinical benefit over modern medical therapy in the large randomized clinical trials powered for clinical outcomes. Obviously, while PCI techniques and outcomes have improved tremendously, this also is the case for medical therapy, which has become remarkably effective. Another consideration to keep in mind is that in both COURAGE and BARI 2D, randomization occurred after patients had undergone coronary angiography and the coronary anatomy had been defined. This opened the door to potential selection of lower-risk patients for revascularization and exclusion of patients with advanced or severe CAD and high risk, the very patients most likely to derive benefit from intervention. Indeed, there is data to support the concept that revascularization may be beneficial in stable CAD, provided the baseline risk and extent of ischemia is sufficient.\textsuperscript{21} The hypothetical benefit of the revascularization procedure over OMT alone is countered by the risk of harm induced by the revascularization procedure itself (such as periprocedural MI, stroke, or stent thrombosis). Hence, it is possible that for revascularization to be superior to OMT in terms of mortality and MI reduction, patients must be above a certain risk threshold that relates mainly to the extent of ischemia, the coronary anatomy, and possibly to clinical characteristics. This will be tested in the upcoming ISCHEMIA trial (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches; ClinicalTrials.gov number NCT01471522).

ISCHEMIA will randomize 8000 patients with documented moderate-to-severe ischemia (involving >10\% of the myocardium) in several hundred sites worldwide to either an invasive strategy plus OMT or to a conservative strategy of OMT alone, in which cardiac catheterization and revascularization will be reserved for patients with refractory angina or clinical events. In contrast with COURAGE and BARI 2D, randomization of patients will be performed before determination of coronary anatomy by angiography in an attempt to minimize any potential selection bias that would exclude higher-risk patients. So far, the only trial to test the value of revascularization that has randomized patients prior to performance of coronary angiography is TIME (Trial of Invasive vs Medical therapy in Elderly patients).\textsuperscript{22} However, in TIME, this resulted in enrolment of some patients who either had too little angiographic disease to warrant revascularization or, conversely, patients whose disease was too extensive to be amenable to revascularization. These concerns will in large part be mitigated in ISCHEMIA, as coronary computed tomography angiography will be performed prior to coronary angiography. This is designed to exclude patients with left main disease and also those without obstructive CAD, to minimize the dilutional impact of randomizing patients to invasive treatment who are not candidates for revascularization.

Because of the focus on myocardial revascularization in the management of CAD, the management of chronic CAD has largely shifted from long-term management of anginal symptoms to a focus on detection and treatment of myocardial ischemia, regardless of whether the ischemia is symptomatic or not. This is based on the concept that myocardial ischemia is prognostic,\textsuperscript{23} and that anginal symptoms are unreliable and correlate poorly with ischemia\textsuperscript{24} or with prognosis, particularly—but not solely—among diabetics.\textsuperscript{25} The dominant view is that ischemia—rather than symptoms—is the main determinant of prognosis,\textsuperscript{26} and it determines the potential benefit derived from revascularization.\textsuperscript{21} A recent analysis from the Heart and Soul Study examined outcomes as a function of the presence or absence of anginal symptoms and myocardial ischemia.\textsuperscript{26} The results showed that relative to patients with neither angina nor ischemia, angina conferred a modest increase in risk, but ischemia—particularly if it was symptomatic—was more important in driving prognosis (Figure 2, page 22).\textsuperscript{24} Indeed, recent studies do suggest that when revascularization is guided by a physiological assessment of coronary anatomy that is able to detect ischemia-generating lesions, such as fractional flow reserve assessment,\textsuperscript{27} revascularization is more likely to improve clinical outcomes.\textsuperscript{28} This has also resulted in a dramatic shift in the clinical presentation of patients with stable CAD. In the past, most patients with chronic CAD suffered from “chronic stable angina,” and physicians spent time and effort in measuring the burden of their angina and prescribing appropriate doses of antiangiinal agents, alone or in combination, to achieve optimal symptomatic relief. Instructions on proper prophylactic and thera-
The CLARIFY registry
Because of these major changes in the clinical presentation, management, and prognosis of patients with stable CAD, collection of representative and contemporary data on the current profiles, management, and outcomes of patients with stable CAD is of key importance. CLARIFY (the prospective observational Longitudinal Registry of patients with stable coronary artery disease) was established as a large-scale prospective international observational registry of outpatients with stable CAD, defined as any of the following 4 criteria (which are not mutually exclusive): history of previous MI (more than 3 months ago), presence of chest pain with objective evidence of myocardial ischemia on noninvasive testing, evidence of angiographic coronary artery stenosis of >50%, or evidence of myocardial ischemia on noninvasive testing, evidence of angiographic coronary artery stenosis of >50%, or evidence of coronary arteriography with >50% stenosis or revascularization with PCI or coronary artery bypass grafting (more than 3 months ago). Patients with stable CAD, defined as any of the following 4 criteria (which are not mutually exclusive): history of previous MI (more than 3 months ago), presence of chest pain with objective evidence of myocardial ischemia on noninvasive testing, evidence of angiographic coronary artery stenosis of >50%, or evidence of myocardial ischemia on noninvasive testing, evidence of angiographic coronary artery stenosis of >50%, or evidence of coronary arteriography with >50% stenosis or revascularization with PCI or coronary artery bypass grafting (more than 3 months ago).

The exclusion criteria were minimized in order to enroll a broadly representative population. Patients were excluded if they had been hospitalized for cardiovascular disease in the previous 3 months, if they had planned revascularization, or if they had conditions hampering participation or follow-up, such as limited cooperation, limited legal capacity, serious noncardiovascular disease, or conditions interfering with life expectancy (such as cancer, drug abuse), or severe cardiovascular disease (e.g., advanced heart failure, severe valve disease, history of valve repair/replacement, etc).

To ensure selection of a population that was representative of stable CAD outpatients, the selection of participating sites involved selection of predefined physician types and practice settings in each participating country. In addition, a short enrolment period was given to each site to enroll a maximum of 15 patients in order to maximize consecutive or near-consecutive enrolment. Finally, to ensure a balanced representation of participating countries, a general target of 25 patients per million inhabitants was used (with a range of 12.5 to 50). Data are being collected anonymously through an annual visit that will take place for up to 5 years of follow-up, with a 6-month phone call between annual visits, in order to maximize follow-up and increase retention rates. Quality control is performed on-site at 5% of sites chosen at random in each country.

At these sites, 100% of case record forms are monitored for source documentation and accuracy. The data are collected and analyzed anonymously by an independent statistics center at the Robertson Center for Biostatistics (University of Glasgow, UK). Recruitment began in November 2009 and concluded in July 2010. Overall, 2898 investigators located at 2343 sites in 46 countries have enrolled more than 33,000 patients. Patients will be followed up on a yearly basis with a clinic visit, with interim 6-month phone calls every year, for up to 5 years. The large size, broad geographic scope, representativeness of the sample, and contemporary nature of the registry are important strengths of the data set.

Some of the baseline results from CLARIFY have already been published: there are important sex-related differences in clinical characteristics and management across all age groups in outpatients with stable CAD. However, although the baseline risk profiles of men and women differ substantially, 1-year outcomes were similar (even though fewer women underwent revascularization). Finally, despite a high rate of use of β-blockers, stable CAD patients frequently have an elevated resting heart rate of ≥70 beats per minute, which, in CLARIFY, is associated with an overall worse health status, more frequent angina, and ischemia.

Another important issue in stable CAD is risk stratification. While several tools exist to allow risk assessment in patients with ACS (such as the GRACE or TIMI [Thrombolysis In Myocardial Infarction] risk scores), there is no such risk engine for patients with stable CAD, with the exception of the REACH (REDuction of Atherothrombosis for Continued Health)
risk score for atherothrombosis, unfortunately, REACH did not include an assessment of heart rate, which has since emerged as a potentially important determinant of outcomes in patients with stable angina. At the end of the CLARIFY follow-up, a robust risk model to predict risk of adverse cardiovascular outcomes will be computed, which will allow incorporation of baseline demographics, clinical and biological examination findings, including heart rate and, if appropriate, key elements of management. This tool will be important to identify those patients with stable CAD who are at high risk, and who may deserve more intensive evaluation and treatment.

References

Keywords: angina, ischemia, prognosis, registry, revascularization
Clarification de l'évolution des tableaux cliniques de la maladie coronaire chronique

Malgré des progrès majeurs pour la prévention et la prise en charge en aiguë de la maladie coronaire (MC), elle reste la première cause de décès dans le monde. Ces 10 dernières années, le tableau clinique et la prise en charge des patients ayant une MC chronique ont considérablement changé. Dans le passé, la prise en charge de ces patients comportait en grande partie la mesure et le contrôle des symptômes angineux, et le dosage soigneux d’un ou plusieurs antiangineux. Néanmoins au fil des années, l’apparition de la revascularisation myocardique, l’amélioration des mesures de prévention secondaire et l’avènement de nouveaux antiangineux puissants ont spectaculairement changé le tableau clinique de la MC chronique. Ces patients sont maintenant en grande partie asymptomatiques, angine de poitrine ou ischémie étant rarement présentes. De plus, si l’angine de poitrine ou l’ischémie sont identifiées, la morphologie coronaire est souvent visualisée par coronarographie en vue d’une revascularisation. Le bénéfice clinique d’une revascularisation banale chez des patients ayant une MC stable reste encore au mieux incertain. L’étude en cours ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) déterminera le bénéfice d’une évaluation anatomique de ces patients par rapport à un traitement médical ordinaire seul. En attendant, le registre observationnel international actuel CLARIFY (prospective observational Longitudinal Registry of patients with coronary artery disease), commencé en 2009-2010 dans 46 pays, collige des informations sur les caractéristiques cliniques, la prise en charge et les résultats (sur 5 ans) d’une grande cohorte (environ 33 000 patients) représentant un large éventail de patients ambulatoires ayant une MC stable. Une analyse en cours décrira la prévalence relative et l’impact pronostique des symptômes angineux et de la présence ou de l’absence d’ischémie myocardique, sur des essais non invasifs.
Patients with stable coronary artery disease (CAD) most often present with effort angina. Angina is an important predictor of cardiac death and hospitalization and to a large extent determines health-related quality of life (QOL) in this patient group. However, the relationship between prognosis and QOL is complex, since asymptomatic patients may be at high risk and QOL may be determined by multiple factors other than angina. Thus, in order to achieve optimal quality of care, treatment goals should include both prevention of clinical events and improvement of QOL. Patients with stable CAD generally have a good prognosis for survival, making QOL even more important. Therefore, QOL assessment should be regarded as an essential measure of the impact of the disease, not only in domains related to physical functioning, but also to psychological well-being and social functioning. Negative disease perception by the patient and poor social support, which may be accompanied by depression or a high level of stress, should always be considered when QOL is assessed. In summary, QOL in CAD patients should be considered as an essential component in patient assessment and follow-up, and should influence the choice of treatment strategy, as well as being a goal per se of management in stable CAD.

Medicographia. 2014;36:25-30 (see French abstract on page 30)

Management standards come from randomized controlled trials (RCTs) that objectively measure the outcomes related to the efficacy and safety of an intervention. Stable coronary artery disease (CAD) is no exception to this rule. However, studies provide statistical data, giving a probabilistic view and describing the impact of treatment on the outcome in the whole study group or in subgroups rather than in an individual subject. It is now generally accepted that the benefits of different treatment strategies and risks related both to the disease itself and to the different therapeutic options should be viewed from an individual patient’s perspective. One should take into consideration not only the physical aspects of the disease, but also the impact it has on mental status and social functioning. These principles are the cornerstone of the “person-centered care” concept that is being dynamically developed in management of different cardiovascular diseases.1

From the patient’s viewpoint, treatment success is determined by 2 factors: survival and quality of life (QOL). Thus, any therapeutic intervention should be aimed at improvement of survival, provision of symptomatic relief, increase in functional activity, and enhancement of overall well-being.

Impact of stable coronary artery disease on quality of life: the patient’s perspective

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“Looking at the disease and its treatment from the patient’s perspective is a matter of increasing significance. Therefore, self-reported health-related quality of life has become an important outcome measure. In patients with stable coronary artery disease, quality of life has to be taken into account to the same degree as the prognostic considerations. Although angina is a major determinant of quality of life, other factors...may play a major role.”

STABLE CORONARY ARTERY DISEASE: AN EVOLVING PICTURE
There is no direct relationship between the real threat and the perceived threat of death. This is especially true in patients with stable CAD. It is due to the fact that patients with stable CAD may have various clinical presentations. Many of them present with angina pectoris, but a significant proportion may be asymptomatic. Angina is an important predictor of cardiac death and hospitalization, and also to a large extent determines health-related QOL. The asymptomatic group includes patients with known CAD, defined as having had a history of myocardial infarction (MI) with or without left ventricular systolic dysfunction; patients after percutaneous coronary interventions (PCI) or coronary artery bypass grafting (CABG); and also patients with diabetes mellitus, whose clinical course is often asymptomatic. The prognosis of asymptomatic patients may vary, and their QOL may depend on symptoms other than angina, eg, heart failure, or be determined by psychosocial factors.

It needs to be emphasized that a substantial proportion of CAD patients also suffer from hypertension, heart failure, diabetes mellitus, chronic obstructive pulmonary disease (COPD), peripheral artery disease (PAD), and other comorbid conditions. Both CAD and comorbidities have an impact on a patient’s clinical outcome and health-related QOL.

While, from the patient’s perspective, prognosis is related to esoteric future events that may or may not happen, QOL refers to the present time and answers the general question: “To what extent does the disease prevent me from living a normal life?” Therefore, QOL is often perceived as more important than prognosis. On the other hand, a threat of coronary hospital admission or death related to CAD, even in low-risk patients, may dominate a patient’s thoughts and dramatically impair QOL. Thus, a comprehensive approach is necessary to take into account the real and the perceived disease burden in stable CAD patients, as health-related QOL is an important health measure and an indicator of outcome.

**Instruments used to measure QOL in patients with stable CAD**

Both disease-specific and generic assessment tools have been used to study QOL in patients with CAD. The Seattle Angina Questionnaire (SAQ) is the most widely used instrument to measure the disease-specific QOL domains in patients with stable CAD. However, not all aspects of QOL are directly related to CAD symptoms. Therefore, the use of general QOL evaluation tools is also warranted in order to have a wider view of the patient’s QOL. Of those tools, the 36-item short-form health survey (SF-36) has the most established role.

The instruments most commonly used to assess health-related QOL in patients with stable CAD are listed in Table I. Kim and Bernstein provide an extensive overview of different tools used to measure QOL in patients with this condition. Here, only the SAQ and SF-36 will be described in more detail.

<table>
<thead>
<tr>
<th>Disease-specific tools</th>
<th>Generic tools</th>
</tr>
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<tbody>
<tr>
<td>Seattle Angina Questionnaire (SAQ)</td>
<td>Medical Outcomes Study 36-item short-form health survey (SF-36)</td>
</tr>
<tr>
<td>MacNew Scale (revised version of the Quality of Life after Myocardial Infarction [QLMI] questionnaire), also known as QLMI-2</td>
<td>McMaster Health Index Questionnaire (MHIQ)</td>
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<tr>
<td></td>
<td>European Quality of Life scale (EuroQol)</td>
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<td></td>
<td>Verbal and visual analog scale</td>
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The SAQ is a self-administered, disease-specific tool comprising 19 questions, evaluating 5 dimensions of health status in patients with CAD, and generating 5 different scales: physical limitation, stability and frequency of angina, treatment satisfaction, and disease perception. In each scale, the worst status or response to treatment on follow-up is assigned 1 point, and the best, 5 points, except for angina frequency, for which the best is assigned 6 points. All scales are treated separately and there is no overall assessment.

**Selected abbreviations and acronyms**

| APPROACH | Alberta Provincial Project for Outcome Assessment in Coronary Heart disease |
| ARTS-II | Arterial Revascularization Therapies Study part II |
| CABG | coronary artery bypass grafting |
| CAD | coronary artery disease |
| CCS | Canadian Cardiovascular Society |
| CLARIFY | Prospective observational Longitudinal Registry of patients with stable coronary artery disease |
| COPD | chronic obstructive pulmonary disease |
| COURAGE | Clinical Outcomes Utilizing Revascularization and Aggressive druG Evaluation |
| EuroQol | European Quality of Life scale |
| HR | heart rate |
| MASS II | Medicine, Angioplasty or Surgery Study |
| MHIQ | McMaster Health Index Questionnaire |
| MOS | Medical Outcomes Study |
| PCI | percutaneous coronary intervention |
| QOL | quality of life |
| SAQ | Seattle Angina Questionnaire |
| SF-36 | short-form health survey [36 items] |
| SIGNIFY | Study assessing the morbidity-mortality benefits of the I3 inhibitor ivabradine in patients with coronary artery disease |
| SYNTAX | SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery |
| TIME | Trial of Invasive versus Medical Therapy in Elderly |
The SF-36 is also self-administered, but is a general QOL assessment tool developed within the Medical Outcomes Study (MOS) and includes 8 health domains reflecting a patient's general functional status and well-being. The 36 questions included in the questionnaire cover such domains as physical, social, and emotional functioning; pain; general health; and vitality. The scores are transformed to a 0-100 scale, with higher values meaning better functioning. The components can be clustered to address the physical and mental aspects of QOL.

The comparison of generic and disease-specific tools has been extensively studied. It appears that the 2 kinds of tools are supplementary rather than competitive. For example, Dougherty et al. compared the usefulness of 3 different tools for QOL assessment in patients with stable CAD receiving medical therapy, in a longitudinal randomized study. The disease-specific SAQ was able to reflect the differences in angina as measured by the Canadian Cardiovascular Society (CCS) grading scale, in all subscales except treatment satisfaction. The SF-36, which is a general tool, not specific to CAD, was able to detect the difference in the CCS class only in the general health subscale. On the other hand, in a group of 253 consecutive patients with CAD followed for 2 years, QOL evaluation using generic instruments was unable to detect an apparent improvement in the CCS class. Although the authors conclude that the major part of health-related QOL is unresponsive to change in chest pain symptoms, their negative results might also have been due to the use of tools that are not sensitive enough to detect a relevant change.

Determinants of QOL in patients with stable CAD

Norris et al. found that age, coronary anatomy, ejection fraction, physical limitation, angina frequency, and gender explain more than 50% of the variance in health-related QOL. Among these factors, physical limitation due to angina and the influence of gender are worth a comment.

It is important to acknowledge that physical disability caused by angina pectoris has an impact on prognosis as well as on QOL. In a cohort of 5558 outpatients with CAD, QOL scores in the domains of physical limitation and angina frequency were found to independently predict all-cause mortality on 1-year follow-up. Odds ratios for mild, moderate, and severe physical limitation were 1.5, 2.0, and 4.0 versus minimal limitation (P < 0.001; Figure 1). For angina frequency, respective values were 0.8, 1.2, and 1.6 (P = 0.078). Hospital admissions for an acute coronary syndrome (ACS) were significantly more frequent in patients with severe angina frequency (P = 0.016). Gender appears to be an important predictor of QOL in patients with CAD. Norris et al. compared the changes in QOL in 3392 male and female patients included in the APPROACH registry (Alberta Provincial PRoject for Outcome Assessment in Coronary Heart disease) at 1 year after the first cardiac catheterization. Using the disease-specific SAQ questionnaire, they found that men reported significantly better health-related QOL than women in all 5 dimensions. They pointed out that sex-related differences cannot be explained by traditional clinical variables, and more research in this area is needed, especially to study psychosocial adjustment of women following treatment of CAD. Worse QOL outcomes in female as compared with male patients have also been reported elsewhere.

Other factors, such as ethnic origin, obesity, mental status, social support, and disease perception, may also have an impact on QOL. However, most important is the fact that resting heart rate (HR), which is a well-established prognostic factor in the general population as well as in patients with CAD, may also be a determinant of QOL in this patient population.

In a large study of CAD patients of different ethnic backgrounds, 1 year after coronary angiography proving the presence of CAD, South Asian patients residing in Canada showed a worse QOL response than subjects of European background. This may be due to the fact that in South Asian individuals, CAD tends to be more diffuse, or may be due to a suboptimal treatment applied in this population.

Obesity negatively affects QOL in patients with CAD. In a large cohort (N=5262) from the APPROACH registry, patients with severe obesity showed significantly lower QOL scores, with...
regard to physical function and overall health-related QOL. Depression symptoms accounted for an important part of this phenomenon. 

Stafford et al. found that depressive symptoms significantly undermine QOL in patients with CAD despite successful revascularization or medical therapy. They suggest that treatment of depression may be a valuable addition to the overall management plan in this patient population. The same phenomenon was reported by Dudek et al., who investigated a group of 156 patients after successful PCI. In the entire study group, QOL up to 1 year post intervention was significantly improved. However, there was a significant correlation between QOL, severity of depressive symptoms, and parameters describing depressive changes in thinking.

Disease perception plays an important role in patients with CAD. In a study of 193 patients recently hospitalized for CAD, Stafford et al. found that negative illness beliefs, particularly those associated with potential consequences of the disease, were predictive of higher levels of depressive symptomatology. On the contrary, positive beliefs led to better QOL outcomes. Older and socially disadvantaged patients had a more negative disease perception, and therefore a close monitoring of this aspect of the illness should be carried out in this group. They can also potentially benefit the most from counseling.

Perceived social support and stressful life events have independent significant effects on QOL in patients with CAD. This is especially important in female patients, in whom both physical and psychological domains were associated with social characteristics, especially with perceived social support.

Resting HR is a well-established risk factor for clinical events in patients with CAD. Andrikopoulos et al. studied a group of 280 patients with CAD and coexisting COPD. They found that subjects with a resting HR >70 beats per minute (bpm) had more frequent angina attacks (P<0.001), were less satisfied with treatment (P<0.001), and had lower QOL (P<0.001). In this specific population, an inadequate HR control was due to the underuse of β-blockers. However, a significant proportion of patients with CAD who receive β-blockers still have suboptimal HR control. In the large contemporary CLARIFY registry (Prospective observational Longitudinal Registry of patients with stable coronary artery disease), comprising over 33,400 patients with chronic stable CAD, 44% had a HR ≥70 bpm. Among almost 25,000 patients treated with β-blockers, over 41% had a HR ≥70 bpm. In this study, a HR ≥70 bpm was independently associated with higher prevalence and severity of angina. One can expect that appropriate HR control may positively alter QOL in these patients.

Whether lowering of HR improves QOL is currently being specifically investigated in a substudy of SIGNIFY (Study assessing the morbidity-mortality benefits of the i, inhibitor ivabradine in patients with coronary artery disease). In SIGNIFY, for which results are expected in 2014, QOL is assessed in patients presenting with angina CCS class II or higher, by means of SAQ and the visual analog scale, based on long-term follow-up.

**Impact of different therapeutic strategies on QOL**

A large number of studies have addressed the impact of different therapeutic strategies on health-related QOL in patients with stable CAD.

In 301 patients with symptomatic CAD aged 75 years and over included in the TIME study (Trial of Invasive versus Medical Therapy in Elderly), QOL was measured at baseline and 6 months after revascularization or administration of optimal medical therapy, using CCS classification, the Rose Angina Score, and the 36-item short-form health survey (SF-36). At baseline, severity of angina significantly correlated with physical domains and daily activities. At the 6-month follow-up, antianginal treatment not only relieved angina and improved physical components, but also lead to an improvement in mental and social domains.

In a large cohort of patients from the APPROACH registry (N=3392), QOL evaluation by SAQ revealed that patients who underwent coronary revascularization (either by CABG or PCI) fared better than those treated medically. It must be emphasized, however, that these findings pertain to the data acquired about 15 years ago and, in light of progress in both drug and interventional therapy, must be interpreted with caution.

More recent research, however, appears to lead to the same conclusions. A post hoc analysis of the MASS II trial (Medicine, Angioplasty or Surgery Study), which randomly assigned CAD patients to CABG, PCI, or medical treatment, revealed that on 1-year follow-up, QOL was better in patients who received revascularization than in those treated medically. CABG patients had a greater and progressive improvement in QOL. The differences were detected even though the assessment tool used was a generic test (SF-36).

Krecki et al reported a better improvement in QOL on 1-year follow-up in patients treated surgically versus those receiving medical treatment. This was true with respect to physical functioning, bodily pain, vitality, mental health, and mental component summary scores, as assessed by the SF-36 questionnaire.

The results of some other studies did not support the view that revascularization is superior to medical treatment in terms of QOL change.

In the COURAGE trial (Clinical Outcomes Utilizing Revascularization and Aggressive drG Evaluation), QOL was assessed in 1 domain only. The SAQ treatment satisfaction score
tended to increase over time both in PCI-treated patients and in those receiving medical treatment. There were no differences between treatment groups over time.

The SYNTAX study (SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery) compared different outcomes in patients with CAD treated with PCI or CABG. QOL was measured at baseline, and thereafter at 1, 6, and 12 months, using SAQ and SF-36 questionnaires. In both groups, scores in all subscales were significantly higher after 6 and 12 months. At the end of follow-up, there were no between-groups differences in physical limitation, treatment satisfaction, and angina stability as measured by SAQ. There was some advantage of CABG with regard to angina frequency and SAQ-assessed QOL, but the absolute differences were small.

Several studies compared the impact of 2 different revascularization methods (CABG and PCI) on QOL. In ARTS-II (the Arterial Revascularization Therapies Study part II), QOL was assessed using the SF-36. This study, conducted for up to 36 months post intervention, showed that both stenting and CABG result in an improvement in QOL and angina severity. With reduction of restenosis rates seen with drug-eluting stents (DES), QOL in this group showed a positive response similar to that observed in CABG patients.

Hlatky et al carried out a very long (10- to 12-year) observation of patients who underwent either CABG or PCI. CABG patients showed a significantly greater improvement in QOL over the first 3 years of follow-up. Afterwards, the advantage of CABG over PCI was no longer present. Recurrent angina was the main factor causing a reduction in all QOL measures throughout the study.

The impact of cardiac rehabilitation programs on the QOL and well-being of patients with CAD is not well established. For example, Tavella and Beltrame studied 221 consecutive patients post coronary intervention. They found an improvement both in disease-specific and generic scores, but no impact of participation in a rehabilitation program on QOL. Michelsen et al studied the effect of a structured stress reduction and modification program on QOL and psychological outcomes. They detected no difference between program participants and patients receiving standard care. Finally, it needs to be emphasized that mood disturbances may have a strong influence on QOL, to the extent that they prevail over the effect of the treatment method itself.

Summary and conclusions
Looking at the disease and its treatment from the patient’s perspective is a matter of increasing significance. Therefore, self-reported health-related QOL has become an important outcome measure. In patients with stable CAD, QOL has to be taken into account to the same degree as the prognostic considerations.

Although angina is a major determinant of QOL, other factors, such as mental status, and the presence of depression in particular, as well as social support, disease perception, or the presence of comorbidities, may play a major role. Medical history taking alone is unlikely to allow an adequate QOL assessment. Thus, special tools should be used for QOL evaluation. Both disease-specific and generic tools are useful in patients with stable CAD. In summary, QOL in CAD patients should be considered as an essential component in patient assessment and follow-up, and should influence the choice of treatment strategy, as well as being a goal per se of management in stable CAD.

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La maladie coronaire (MC) stable se manifeste le plus souvent par un angor d’effort. L’angine de poitrine est un prédicteur important de décès et d’hospitalisation pour cause cardiaque et détermine en grande partie la qualité de vie (QDV) liée à la santé dans ce groupe de patients. Les rapports entre le pronostic et la QDV sont cependant complexes, les patients asymptomatiques pouvant être à haut risque et la QDV déterminée par de multiples facteurs autres que l’angine de poitrine. Ainsi, pour assurer une qualité des soins optimale, les objectifs de traitement doivent associer la prévention des événements cliniques et l’amélioration de la QDV. Le pronostic de survie des patients ayant une MC stable est généralement bon, ce qui rend la QDV encore plus importante. Son évaluation doit donc être considérée comme une mesure essentielle de l’impact de la maladie, non seulement dans le domaine fonctionnel physique, mais aussi dans celui du bien-être psychologique et du fonctionnement social. Une perception négative de la maladie par le patient et un mauvais soutien social, pouvant s’accompagner d’une dépression ou d’un stress important, doivent toujours être pris en compte en évaluant la QDV. En résumé, la QDV des patients coronariens est un composant essentiel de l’évaluation et du suivi du patient qui doit non seulement déterminer le choix de la stratégie thérapeutique mais être considérée comme un objectif à part entière de la prise en charge de la MC stable.
A large body of evidence conclusively suggests that the close link traditionally assumed between coronary stenosis and myocardial ischemia is no longer tenable. It appears that it would be much more realistic to regard ischemic heart disease as a multifactorial syndrome, considering that several mechanisms can contribute to precipitating myocardial ischemia, including inflammation, coronary spasm, microvascular dysfunction, endothelial dysfunction, platelet activation, and coronary stenosis.

Current guidelines consider obstructive atherosclerotic coronary artery disease to be the most common cause of chronic stable angina, to the point that the terms obstructive coronary artery disease and ischemic heart disease are interchangeably used. However, a large body of accumulating evidence challenges this view: (i) coronary atherosclerotic obstructions are not consistently present in angina patients; (ii) coronary stenosis does not have a predictable impact on myocardial perfusion; and (iii) stenosis removal is not consistently effective in curing angina pectoris and does not have an impact on prognosis in patients with chronic ischemic heart disease. Altogether, these data strongly support the hypothesis that ischemic heart disease is a multifactorial syndrome, with coronary stenosis being just one of the many mechanisms that can precipitate myocardial ischemia in man. A better understanding of the nature and prevalence of these mechanisms could provide the basis for a tailored approach to therapy in patients with stable angina/chronic ischemic heart disease.

Ischemic heart disease (IHD) is a leading cause of mortality and, among others, stable angina represents the most frequent clinical presentation. The annual incidence of uncomplicated angina pectoris is estimated at around 0.5%, with a prevalence ranging from 20,000 to 50,000 per 1 million in Western general populations aged over 40.

According to major guidelines, obstructive atherosclerotic coronary artery disease (CAD) is regarded as the most common cause of chronic stable angina, with nonobstructive CADs (i.e., vasospastic angina and X syndrome) being considered only rare conditions that do not deserve particular attention. Current understanding of the pathophysiological basis of myocardial ischemia is derived from experimental observations that coronary artery narrowing limits resting and hyperemic coronary blood flow. These concepts have been further extended, with the current paradigm delineating the atherosclerotic plaque as the target of both diagnostic protocols and therapeutic strategies. As a consequence, “the search for and treatment of obstructive CAD” is viewed as the crucial aspect in the management of patients with suspected IHD, with cardiologists, as pointed out in a recent paper by Rothberg, being viewed more or less as “pipe” specialists. Nonetheless, overt clinical inconsistencies and the prohibitive costs associated with the current approach, together with the disappointing results with regard to hard events (mortality, myocardial
dial infarction), suggest the need for reconsidering longstanding views. Indeed, while in everyday practice CAD is regarded as synonymous and equivalent to IHD, a growing body of evidence strongly challenges this concept, supporting the need for an innovative approach to IHD, focused on myocardial ischemia more than on coronary atherosclerotic plaques. In this review, we will report on recent evidence suggesting that the link between coronary atherosclerotic obstructions and IHD is much more elusive than we have believed so far.

Are coronary atheromatous obstructions consistently present in angina patients?

In a recent study involving 397,954 subjects referred for cardiac catheterization, Patel et al tested the effectiveness of current criteria in predicting obstructive CAD and compared the prevalence of coronary stenosis ≥50% with the result of provocative tests. A positive test result was recorded in 68.6% of all the patients in the cohort. At angiography, a much smaller fraction, 37.6%, was found to have coronary obstructive lesions. Even more surprisingly, the prevalence of coronary stenosis ≥50% was similar in all groups, including patients with a positive test result, patients with an equivocal result, patients with a negative result, and in patients that had not undergone the test, suggesting the absence of any consistent association between prevalence of CAD stenosis ≥50% and inducible myocardial ischemia. Interestingly enough, a linear relationship was observed between the Framingham Risk Score (FRS) and the prevalence of coronary stenosis, with patients with higher scores more likely to have obstructive CAD.6 Based on this data, the question arises whether established coronary risk factors are indeed predictive of coronary atherosclerosis more than of IHD.

Consistent observations have been reported in the CONFIRM study (Coronary computed tomography angiography evaluation for clinical outcomes: an Intergenational Multicenter study).7 The investigators compared the pretest probability of angiographically significant CAD as estimated by current guidelines with the prevalence observed at coronary computed tomography (CT) angiography. The study included 12,797 patients. There were 7113 men and 5684 women analyzed on the basis of clinical symptoms of myocardial ischemia: patients with typical angina, patients with atypical angina, patients with nonanginal chest pain, and asymptomatic patients.

In all patient groups of both sexes, the prevalence of coronary stenosis was linearly related to age (Figure 1).1 Unexpected findings included (i) a much lower prevalence of obstructive CAD in patients with typical angina than predicted by guidelines, ranging from 25%-45% in men and 10%-25% in women (Figure 1) and (ii) a prevalence of obstructive CAD at CT angiography that was similar in all patient groups, from totally asymptomatic patients to typical angina patients (Figure 1). Based on these observations, 2 conclusions can be drawn. Firstly, most patients with angiographically significant coronary stenosis do not have angina. Secondly, less than 50% of older men with typical angina and less than 30% of older women with typical angina have an angiographically significant coronary stenosis. Obviously, one has to ask why so many patients with a significant coronary stenosis do not have symptoms or other evidence of IHD and what causes angina in patients free from obstructive CAD. Certainly, these data strongly challenge the popular concept that angina is consistently associated with significant obstructive CAD. Actually, these observations are not entirely new: inducible ischemia in the absence of obstructive CAD has long been documented.6,8 Conversely, patients with normal stress single-photon emission CT (SPECT) images have been reported to have obstructive CAD detected by CT coronary angiography (CTA).9 However, these contradictory observations have been traditionally attributed to a low predictive value of noninvasive imaging techniques.6 Given the consistency of these observations, the evidence has been accepted with time: angina can frequently occur in the absence of significant coronary stenosis, and most subjects with obstructive CAD simply do not suffer from myocardial ischemia.

Does coronary stenosis have a predictable impact on myocardial perfusion?

In contrast with the linear model originally proposed by Gould et al,10 the relationship between stenosis severity and coronary myocardial blood flow is characterized by wide scatter on scatterplot analysis, and direct transfer to the clinical setting appears overly simplistic.11,12 Naya et al13 sought to determine the effects of coronary atherosclerosis morphology and extent, assessed by CTA, on myocardial flow reserve (MFR), evaluated by poston emission tomography. The authors found that severity of stenosis by CTA had only a modest effect on downstream MFR. Indeed, stenosis severity did not reliably

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**Selected abbreviations and acronyms**

- CAD: coronary artery disease
- CONFIRM: CoroNary computed tomography angiography evaluation For clinical outcomes: an Intergenational Multicenter study
- COURAGE: Clinical Outcomes Utilizing Revascularization and Aggressive drug Evaluation
- CT: computed tomography
- CTA: computed tomography coronary angiography
- FFR: fractional flow reserve
- FIRST: Fractional flow reserve and Intravascular ultrasound Relationship study
- FRS: Framingham Risk Score
- IHD: ischemic heart disease
- IVUS: intravascular ultrasound
- MFR: myocardial flow reserve
- MLA: minimal lumen area
- PCI: percutaneous coronary intervention
- SAQ: Seattle Angina Questionnaire
predict physiological myocardial blood flow effects. More specifically, they found that patients with 0% stenosis diameter or 0 summed stenosis score by CTA could present with a MFR ranging from 1 to 5, and, on the other hand, that patients with ≥70% stenosis diameter or higher summed stenosis score could have a normal MFR.

Kang et al assessed the accuracy of intravascular ultrasound (IVUS) in predicting the functional significance of intermediate coronary lesions. In this study, 201 patients, with a total of 236 coronary lesions, underwent IVUS and invasive physiological assessment with fractional flow reserve (FFR) before intervention. The authors identified an IVUS minimal lumen area (MLA) of ≥2.4 mm² as a cutoff with high predictive value for an FFR ≥0.8. However, 63% of lesions with an MLA <2.4 mm² had an FFR ≥0.8, and the results were similar when other IVUS-measured parameters were related to FFR. These observations imply that, in the individual patient, it is impossible to estimate the physiological impact of a coronary stenosis from its cross-sectional area, however accurately it is measured. In other words, stenosis anatomy is not a reliable predictor of stenosis physiology.

Similarly, FIRST (Fractional flow reserve and Intravascular ultrasound RelationShip sTudy) investigators sought to determine the optimal MLA correlating with FFR and correlation between virtual histology IVUS and FFR for intermediate coronary lesions. This was a multicenter, prospective, international registry involving 350 patients with intermediate coronary lesions at angiography. An MLA <3.07 mm² was identified as the best threshold value for identifying FFR <0.8. However, this finding was shown to be dependent on vessel diameter.

On the other hand, FFR correlated with plaque burden, but not with other plaque parameters, thus questioning the clinical utility of IVUS MLA, hence of coronary anatomy, in predicting myocardial perfusion.

**Figure 1.** Prevalence of coronary stenosis predicted by current guidelines (dark bars) and observed at computed tomography angiography (light bars) in asymptomatic, nonanginal chest pain, atypical angina, and typical angina patients.

**Abbreviations:** CAD50, coronary artery disease with ≥50% diameter stenosis.


**Figure 2.** Prevalence of angina following “successful” coronary revascularization.

**Abbreviations:** BARI, Bypass Angioplasty Revascularization Investigation; CABG, coronary artery bypass grafting; CABRI, Coronary Angioplasty versus Bypass Revascularization Investigation; EAST, Emory Angioplasty versus Surgery Trial; PTCA, percutaneous transluminal coronary angioplasty; RITA, Randomized Intervention Treatment of Angina.
Is stenosis removal consistently effective in curing angina pectoris?

Large clinical trials have reported that following coronary revascularization, many patients present with persistent symptoms (Figure 2, page 33). \(^{16-22}\) In a recent comparison of medical therapy and medical therapy plus percutaneous coronary intervention (PCI) in the COURAGE trial (Clinical Outcomes Utilizing Revascularization and Aggressive drUG Evaluation), about one-third of patients still complained with angina at the 1-year follow-up, with a minor difference between those whose stenosis had been removed (PCI branch) and those whose stenosis had not been removed (medical therapy branch) (Figure 3). \(^{21}\)

We conducted a single center, prospective, observational study on a highly selected, chronic angina patient population undergoing successful and complete PCI with a preprocedural positive exercise stress test. We made an effort to avoid all confounding factors (ie, patients with valvular dysfunction, primary cardiomyopathy, etc). \(^{23}\) Of the 220 patients included in the study, nearly 50% still had positive exercise stress test results at 1 month after the index PCI (Figure 4). \(^{23}\) A similar rate for positive stress test results were found at 6- and 12-month follow-up visits. Most importantly, one-third of the total population also had effort angina with impaired quality of life as assessed by the Seattle Angina Questionnaire (SAQ). As the stenosis had been removed, what was the cause of persisting symptoms/ischemia in these patients?

Does stenosis removal have an impact on prognosis?

When compared with medical therapy, neither the advent of PCI itself \(^{16,17,21}\) nor the progressive sophistications of percutaneous techniques \(^{24}\) have changed the mortality and morbidity of patients with chronic IHD.

Recently, De Bruyne et al \(^{25}\) reported on the efficacy of FFR-guided PCI versus medical therapy in 1220 patients with stable CAD. Among patients deemed in stable condition and considered appropriate candidates for PCI, about one-third was found not to have a significant coronary stenosis. The patients found to have a significant coronary stenosis, based on a FFR below 0.80, were randomized to PCI plus medical therapy or medical therapy alone. Similar to what was observed in the COURAGE trial, \(^{21}\) PCI had no impact on mortality and morbidity, and the rate of revascularization was the only outcome that significantly differed between treatment groups. Patients in the PCI group underwent 14 additional procedures during the follow-up; patients initially treated medically underwent 86 procedures. Half of the procedures at follow-up were rated as urgent in both groups. According to these results, following stenosis assessment with FFR, 12 patients with significant obstructions need to be treated in order to prevent 1 unplanned revascularization procedure. In this way, one would unnecessarily and prematurely expose 11 patients to revascularization-related adverse effects (ie, early and late stent thrombosis), an aspect that could not be assessed in the present work due to the short follow-up period. Considering that an initially invasive strategy does not change patient outcome in terms of death and myocardial infarction, wouldn’t it be more prudent and cost-effective to manage patients medically until “unplanned revascularization” is needed, if ever?

What dictates prognosis: coronary atherosclerosis or myocardial ischemia?

Despite scant evidence, patients with chest pain and no obstructive CAD have been traditionally considered at low risk for cardiovascular events. In recent work, Jespersen et al assessed the prognostic implications of angina pectoris in relation to the presence and degree of CAD. \(^{26}\) Major adverse cardiovascular events of 11 223 patients with stable angina pectoris, referred for coronary angiography from 1998 to 2009, were compared with 5705 controls without IHD. In line with
previous studies, significantly more women (65%) than men (32%) had nonobstructive CAD on coronary angiography. In addition, the risk of major cardiovascular events increased linearly with increasing CAD burden (hazard ratio, 1.52 for patients with normal coronary arteries and 1.85 for patients with diffuse nonobstructive CAD). However, angina patients with no coronary atherosclerosis had a higher rate of major adverse events when compared with the reference population. Thus, while both CAD burden and angina appear to be linear predictors of major cardiovascular events, the most fragile link appears to be the one between obstructive CAD and angina. In line with these considerations, in a recent review paper, Roberts et al pointed out that despite the confusion generated by using CAD and myocardial infarction phenotypes interchangeably, genetic studies show that risk alleles for CAD and myocardial infarction do not display associative properties.

In conclusion, a large body of evidence conclusively suggests that the close link traditionally assumed between coronary stenosis and myocardial ischemia is no longer tenable. It appears that it would be much more realistic to regard IHD as a multifactorial syndrome, considering that several mechanisms can contribute to precipitating myocardial ischemia, including inflammation, coronary spasm, microvascular dysfunction, endothelial dysfunction, platelet activation, and coronary stenosis, etc.

Myocardial perfusion is modulated by complex regulatory mechanisms adjusting blood flow volume, blood flow velocity, and blood flow pressure. Additionally, myocardial ischemia, defined as an imbalance between energy supply and demand, is an even more complicated issue. Delivering an adequate amount of oxygenated blood, at the right pressure and at the right velocity, to cardiomyocytes is just the beginning of the journey. Energy substrates delivered to cardiac cells in adequate amounts must be transported inside the cells, incorporated by the mitochondria, transformed into high-energy phosphate bonds that in turn must be delivered to the contractile machinery where they are eventually transformed into work and heat. Any dysfunction in this long and complex sequence of events may cause an imbalance in myocardial energy demand and supply. In other words, myocardial ischemia. Indeed, just as a combustion engine with a perfect injection mechanism, the cardiomyocyte may run short on fuel, due to intracellular dyshomoeostasis (i.e., altered mitochondrial metabolism, dysfunction of extracellular matrix, barriers to oxygen transport, etc.).

With this approach in mind, assuming ischemia to be a problem of "clogged pipes" is clearly an overly simplistic view. A better understanding of the nature and prevalence of the mechanisms underlying IHD may provide the basis for advancement toward tailored therapy in patients with stable angina/chronic ischemic heart disease.

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Keywords: atherosclerosis; ischemic heart disease; multifactorial; stenosis

**REPENSER LA PHYSIOPATHOLOGIE DE LA MALADIE CORONAIRE STABLE**

D’après les recommandations actuelles, la maladie coronaire athéroscléreuse obstructive est la cause la plus courante d’angor stable chronique, au point que les termes de maladie coronaire obstructive et cardiopathie ischémique sont interchangeable. Cet avis est néanmoins remis en question par de plus en plus de données ; par exemple, 1) les obstructions coronaires athéroscléreuses ne sont pas présentes de façon constante chez les patients angoreux ; 2) l’impact de la sténose coronaire sur la perfusion myocardique n’est pas prévisible; et 3) l’ablation de la sténose ne supprime pas toujours l’angor et n’influe pas toujours sur le pronostic des patients ayant une maladie coronaire chronique. Globalement, ces données soutiennent fortement l’hypothèse que la maladie coronaire est un syndrome multifactoriel, la sténose coronaire n’étant qu’un des nombreux mécanismes pouvant accélérer une ischémie myocardique chez l’homme. Une meilleure compréhension de la nature et de la prévalence de ces mécanismes permettrait de mieux fonder un traitement personnalisé des patients ayant un angor stable ou une maladie coronaire chronique.
Experimental models of atherogenesis continue to contribute to elucidation of the molecular mechanisms behind plaque growth; however, the transition from coronary stability to instability is less well understood due to the lack of animal models reflective of human disease. The abrupt onset of acute coronary syndromes (ACS) is a strong indication of discontinuity in the progression of atherothrombosis. The causes of such discontinuity are complex, probably multiple, and still largely unknown. The complexity of postmortem and clinical observations suggests that it is unlikely that a common cause will be identified for the phenotype of ACS. To better understand the multiple causes of coronary instability, it would be desirable to construct a pathogenetic classification of ACS based on simple clinical descriptors. In this review, the multiple causes of coronary instability are discussed in 3 homogeneous groups of patients with a similar clinical presentation: (i) patients who have obstructive atherosclerosis and systemic inflammation, (ii) patients who have obstructive atherosclerosis without systemic inflammation, and (iii) patients with functional alterations of coronary circulation. Such classification of ACS provides a framework for understanding basic mechanisms responsible for coronary instability rather than a classification for immediate clinical use, such as that provided by the universal definition of myocardial infarction. However, our pathogenetic classification of ACS based on simple clinical descriptors might help in the search for new diagnostic algorithms and therapeutic targets.

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Atherosclerotic vascular disease is the leading cause of death in Western countries; among the different manifestations of disease, the acute coronary syndromes (ACS) play the major role. The pathogenesis of ACS is complex and not fully clarified, whereas mechanisms leading to atherosclerotic plaque growth have been better characterized, allowing an improvement in primary prevention. In particular, transition from coronary stability to instability should be better investigated with the aim of preventing acute events when primary prevention measures fail. Interestingly, clinical instability is heterogeneous from many points of view. Indeed, whereas some patients have 1 episode of ACS that will not recur during their lifetime, others have multiple (ie, recurrent) episodes. Additionally, some cases are associated with severe stenosis and others, with mild-to-moderate lesions; thus, plaque severity leading to acute coronary syndrome is heterogeneous, as are plaque morphology and composition. Indeed, postmortem studies and, recently, intravascular imaging have shown that ACS can be associated with plaque rupture, plaque ero-
Pathophysiology of ACS

Plaque rupture associated with thrombosis is the most frequent plaque feature in patients with ACS.6,7 This observation has been obtained in the postmortem setting,1 but also in vivo by using intravascular ultrasound,2 angioscopy,3 and more recently, optical coherence tomography (OCT).4-11 In particular, OCT, with its high resolution, recently clarified that in vivo plaque rupture is associated with ACS in 75% of ST-elevation myocardial infarction (STEMI) patients.1 As suggested by postmortem4,12 and in vivo studies,13-14 the precursor of a ruptured plaque is a thin-cap fibroatheroma (TCFA), containing a large necrotic core covered by a thin, fibrous cap characterized by the presence of activated macrophages. TCFA have been found to be associated with a higher risk of ACS using both noninvasive and invasive imaging modalities.15-16

It is worth noting, however, that rupture of TCFA may not necessarily lead to ACS, as asymptomatic plaque rupture is a frequent event leading to plaque progression.17-19 The reasons why some plaque ruptures lead to ACS and others do not are largely unknown. Mechanisms leading to plaque rupture may be classified according to levels of systemic markers of inflammation.20 Indeed, some patients exhibit marked elevation of inflammatory biomarkers, and widespread coronary microvascular and myocardial inflammation with activation of innate and adaptive immunity,21,22 while others have measurable levels of inflammatory biomarkers, suggesting mechanisms other than sustained inflammation.23

Plaque rupture with activation of systemic inflammation

Several studies have shown that systemic inflammation, as assessed by C-reactive protein (CRP), plays a crucial role in the process of coronary instability.24-26 In particular, it has been found that inflammatory mechanisms regulate the fragility of the fibrous cap, as well as the thrombogenic potential of the lipid core.26-27 Ruptured plaques and vulnerable plaques, compared with intact plaques, have larger numbers of inflammatory cells, mostly monocyte-macrophages, but also T cells, eosinophils, and mast cells. These inflammatory cells, showing evidence of activation,38-39 are mostly located in the shoulders of the fibrous caps and in the lipid core as well as in the adventitia around areas of neovascularization.30-31 The latter might contribute to the recruitment of inflammatory cells in atherosclerotic plaques. Inflammatory activation is not confined to the culprit stenosis, as suggested by the observation of widespread neutrophil activation in the coronary circulation of patients with unstable angina32 and by the presence of activated T lymphocytes in remote unaffected myocardial regions33 in approximately two-thirds of patients with recent myocardial infarction (MI).34 Moreover, investigating all major coronary artery branches by intravascular ultrasound, Rioufol et al observed multiple ruptures in patients with a first ACS.35

Among cells of the innate immunity, neutrophils and macrophages play a major role. Interestingly, the activation of neutrophils in the coronary circulation is suggested by telomerase activation in neutrophils from the culprit coronary plaques of patients with ACS, but not in neutrophils from plaques of patients with stable angina.33 The reactivation of telomerase, demonstrated in the early phases of coronary instability, delays cell apoptosis, thus favoring persistence of inflammation.34 Neutrophil activation in ACS appears to be an early and short-lasting event.35

The predominant inflammatory cells in atherosclerotic plaques are macrophages recruited as monocytes from circulating blood. There are different subsets of monocytes with different gene expression patterns and, in particular, differential expression of CD14 and CD16.36,37 The amount of CD14+CD16+ monocytes in patients with coronary atherosclerosis is higher as compared with that in healthy subjects and peak levels of CD14+CD16+ monocytes after acute MI correlate negatively with the recovery of left ventricular ejection fraction 6 months after MI.38 Moreover, macrophages are probably involved in the rupture of the fibrous caps as they produce larger amounts of matrix metalloproteinases (MMPs).39-41 enzymes that degrade all components of the extracellular matrix.42 The production and activation of MMPs are regulated at the level of gene transcription and by the cosecretion of tissue inhibitors of MMPs (TIMPs). Thus, increased gene transcription of MMPs or re-
duced activity of TIMPS can enhance matrix proteolysis. It has been shown that Toll-like receptors (TLR) may mediate the activation of monocytes-macrophages; indeed, monocytes accumulated within thrombi, obtained during primary percutaneous coronary interventions, specifically overexpress TLR4, together with specific patterns of locally expressed chemokines and cytokines, compared with circulating monocytes.\textsuperscript{43-46} Notably, Niessner et al\textsuperscript{45} have confirmed enhanced TLR4 in carotid plaques, probably mediated by interferon $\alpha$ released by plasmacytoid dendritic cells, specialized in sensing danger signals from bacteria and tissue breakdown.\textsuperscript{45} Thus, all components leading to activation of the MMP pathway are present in the atherosclerotic plaques. A recent study by Blair et al demonstrated that human platelets also express functional TLRs\textsuperscript{46}; TLR2, in particular, promotes platelet-leukocyte interactions, amplifying platelet-derived inflammatory signals. In this prospective, platelets act as coprotagonists in plaque activation and as a major player in the thrombotic processes. Moreover, Beaulieu et al\textsuperscript{47} have shown TLR2 expression on megakaryocytes and suggested that inflammation through TLR2 stimulation can increase megakaryocyte maturation and modulate megakaryocyte phenotype, potentially influencing platelet function and thrombosis.

The involvement in coronary instability of cells of adaptive immunity has consistently been demonstrated with studies reporting enhanced activation of T cells in patients with ACS as compared with those with stable angina,\textsuperscript{21-22} and oligoclonal porting enhanced activation of T cells in patients with ACS as stable plaques.\textsuperscript{21,48} Based on the notion that the activation of T cells requires a specific antigen stimulation mediated by antigen-presenting cells, some studies have identified candidate antigens, like Chlamydia pneumoniae, heat shock proteins, or oxidized low-density lipoproteins (oxLDLs), in plaques from patients with ACS.\textsuperscript{55} Accordingly, CD4$^+$CD28$^-$ T cells, so called for the defective cell surface expression of CD28, a major costimulatory molecule critically involved in determining the outcome of antigen recognition by T cells, have been found to undergo clonal expansion in unstable coronary plaques, where they release potent proinflammatory cytokines (mostly interferon $\gamma$), enhancing activation of innate immunity cells—and to have direct cytolytic effects on endothelial cells, amplified by high-sensitivity CRP (hs-CRP),\textsuperscript{49} and on vascular smooth muscle cells.\textsuperscript{50} Thus promoting plaque rupture.\textsuperscript{51} Of note, both circulating and resident CD4$^+$CD28$^-$ T cells spontaneously express interleukin (IL)-12 receptor and respond to IL-12 released by innate immunity cells with the upregulation of chemokine receptors; thus, IL-12 can favor tissue homing of CD4$^+$CD28$^-$ T cells even in the absence of antigenic stimulation.\textsuperscript{52}

Although their precise role in atherosclerosis remains controversial, recent studies have shown a proatherogenic role of another lymphocyte subset represented by T helper 17 (Th17) cells; they produce IL-17 involved in autoimmune and allergic reactions.\textsuperscript{53} CD4$^+$CD25$^+$ regulatory T cells (Treg) also are profoundly perturbed in ACS. The normal functioning of Treg is essential to maintain the homeostasis of T-cell subsets involved in adaptive immunity. Accordingly, Treg expressing the forkhead/winged-helix transcription factor Foxp3 have been found to prevent atherosclerosis in mouse models.\textsuperscript{54} Consistently, a critical role for the anti-inflammatory cytokine IL-10 has been assumed in Treg-mediated atheroprotection, both in experimental models and in human atherosclerotic lesions, where Treg and IL-10 expression are colocalized. The balance between Th17 and Treg cells may be important in the development and prevention of inflammatory and autoimmune diseases.\textsuperscript{55} Recently published data provide evidence of a defective Treg compartment in ACS. The number and the suppression efficiency of Treg were reduced in patients with ACS compared with patients with stable angina and healthy controls.\textsuperscript{56} A parallel increase in the circulating levels of Th17 has also been observed.\textsuperscript{57} Taken together, these observations suggest that, at least in a subset of patients with ACS, the reduction of a counterregulatory response to the activation of aggressive effector T cells might play a key pathogenetic role and may become a potential therapeutic target.\textsuperscript{58}

\textbf{Plaque rupture without activation of systemic inflammation}

When plaque rupture occurs in the absence of systemic inflammatory activation, other mechanisms, including emotional and physical stress or changes in plaque composition may play a pathogenetic role.\textsuperscript{53} The ability of systemic stress to induce plaque rupture is related to sympathetic nervous system activation and catecholamine release associated with increase in heart rate, blood pressure, and coronary vasoconstriction favoring the rupture of vulnerable plaques\textsuperscript{59} and to platelet activation, hypercoagulability, and intense coronary microvascular constriction.\textsuperscript{60} It has been demonstrated that the highest stress is present in the shoulder region of the fibrous cap.\textsuperscript{61}

Changes in plaque composition have been hypothesized by Abela et al\textsuperscript{52} as a possible cause of plaque rupture. Indeed, local changes in pH, temperature, cholesterol saturation, and hydration promote cholesterol crystallization in the lipid core, associated with quick volume expansion, potentially causing plaque fissure and thrombosis. This mechanism may be amplified by crystallization of free cholesterol from erythrocyte membranes when intraplaque hemorrhage occurs.\textsuperscript{62}

\textbf{Plaque erosion}

Plaque erosion is reported in at least one-third of patients dying of acute MI in postmortem histopathological studies.\textsuperscript{4} Coronary instability is assumed to be the result of plaque erosion if there is no continuity between the thrombus and the necrotic core and the thrombus is in direct contact with the fibrointimal plaque.\textsuperscript{63} On OCT analysis, plaque erosion consists of evidence of thrombi, an irregular luminal surface, and no evidence of cap rupture evaluated in multiple adjacent frames.
Neutrophil activation seems to play a pivotal role in plaque erosion. We have recently showed that patients presenting with ACS associated with plaque erosion had higher systemic myeloperoxidase levels as compared with levels in patients exhibiting plaque rupture.6 Moreover, in postmortem coronary specimens, luminal thrombi superimposed on eroded plaques contained a much higher density of myeloperoxidase (MPO)-positive cells than thrombi superimposed on ruptured plaques.6 One study6 reported an intense immunostaining pattern for hyaluronan and its receptor, CD44, along the plaque/thrombus interface in eroded plaque, but not in fissured or stable plaque. Accumulation of hyaluronan and expression of CD44 along the plaque/thrombus interface of eroded plaques may promote de-endothelialization, resulting in CD44-dependent platelet adhesion and subsequent thrombus formation, in part mediated by a direct action of hyaluronan on fibrin polymerization. Furthermore, accumulation of hyaluronan in eroded plaques may promote CD44-dependent adhesion and accumulation of circulating neutrophils and MPO-expressing monocytes, which in turn may enhance endothelial cell death and promote thrombus formation. MPO, released by neutrophils, catalyzes the formation of MPO-derived reactive species (MDRS), such as hypochlorous acid (HOCl), using chloride, thiocyanate, or nitric oxide (NO) as the substrate and hydrogen peroxide as the cosubstrate. MDRS are responsible for consuming NO, which may result in impaired vasodilation, oxidation of LDL and high-density lipoprotein, activation of MMPs, oxidation of proteoglycans and glycosaminoglycans, and apoptosis of endothelial cells by activation of a specific pathway. Furthermore, activated neutrophils shed microparticles, which may transfer tissue factor into platelets, thus contributing to thrombosis. Tissue factor expression and activation is also induced by MDRS and oxLDL.66 MPO may also have a role in thrombus growth.67-68

Finally, calcified nodules, found to be more frequent in patients with diabetes,69 are a less common cause of coronary instability. They are lesions with the highest concentration of calcification relative to plaque area and can be a rare trigger for thrombosis.4

**Vasoconstriction of epicardial vessels or microcirculation**

Epicardial coronary vasospasm is likely to play a key role in ACS, particularly in patients in whom coronary angiography fails to demonstrate the presence of an obstructive atherosclerotic plaque.6 In such patients, the incidence is about 50% as reported in the CASPAR study (Coronary Artery Spasm in Patients With Acute Coronary Syndrome)73 in patients with ACS and about 50% as reported by the ACOVA study (Abnormal Coronary Vasomotion in patients with stable angina and unobstructed coronary arteries) in patients with stable angina.71 Coronary spasm is caused by vasoconstrictor stimuli acting on hyperreactive vascular smooth muscle cells, perhaps because of enhanced Rho-kinase activity.72 Spasm can occur at the site of an angiographically normal coronary segment or in the presence of a nonobstructive atherosclerotic plaque.73 Unpublished data by our research group show that ACS patients with smooth plaques without thrombus on OCT investigation have elevated cystatin C levels in agreement with data by Funayama et al74 showing elevated cystatin C levels in patients with vasospastic angina.

Vasoconstriction causing ACS also occurs at the microvascular level.75-78 In particular, intense coronary microvascular vasoconstriction plays an important role in the pathogenesis of Takotsubo syndrome,77 characterized by ischemic pain at rest, ST-segment elevation, cardiac enzyme release, and a characteristic regional akinesia more frequently affecting distal myocardial regions associated with hypercontractility of the remaining regions.

Finally, Mohri et al have described a clinical presentation of ACS characterized by chest pain, ST-segment elevation, normal epicardial coronary arteries, and normal myocardial function.78 As acetylcholine provocation testing reproduced the same symptoms and electrocardiographic alterations in the absence of epicardial vasospasm, the authors proposed that the cause of this syndrome was coronary microvascular spasm.

**Clinical implications**

Table I and Figure 1 summarize pathogenetic mechanisms of ACS along with diagnostic and therapeutic options tailored for individual mechanisms of coronary instability. Several studies have shown that patients with ACS in whom obstructive atherosclerosis is associated with elevated levels of CRP or other markers of inflammation have a worse outcome than patients with a similar severity of coronary atherosclerosis, but normal levels of inflammatory markers.14,32,79-82 Thus, in the former, reassessment of the inflammatory status after discharge may help in the identification of patients at higher risk of recurrence of coronary instability. Although the assessment of the inflammatory status is currently based on biomarkers only, recently developed imaging techniques able to monitor inflammatory cell activity in atherosclerotic plaques might prove to be more predictive than biomarkers.83 In addition, an unmet need in this patient subset is a specific anti-inflammatory treatment based on the modulation of both innate and adaptive immunity.24,84-86

In patients with ACS in whom plaque fissure is not associated with systemic inflammation, anatomic (more than functional) features of the atherosclerotic plaque are important in determining coronary instability. Because it is difficult to limit environmental, physical, or emotional triggers, an obvious target in this patient subset is plaque stabilization as achieved by intensive statin treatment.86 Inhibitors of phospholipase A2 represent another class of drugs that might help in plaque stabilization. Another important, but still elusive target to promote plaque stabilization is enhancement of cholesterol efflux.87 Among patients in whom plaque fissure is not associated with
systemic inflammation and in whom ACS occurs in the absence of environmental, physical, or emotional triggers, more needs to be learned about the mechanisms modulating cholesterol crystallization, including the inflammasome pathway activated by cholesterol crystals, in order to identify new therapeutic targets.

In patients with plaque erosion, the mechanism of inflammation is probably an intense local thrombogenic stimulus. Thus, in this subset of patients, a potent antithrombotic treatment perhaps based on double antiaggregation and an oral anticoagulant might be the treatment of choice, but this approach needs to be tested in prospective studies.
Finally, epicardial and microvascular vasoconstriction is the key therapeutic target when ACS is not associated with obstructive atherosclerosis. Recently, data from clinical trials suggest that the outcome of these patients is, on average, better than that of patients with obstructive atherosclerosis; however, about 10% of patients presenting with ACS in the absence of coronary atherosclerosis had had a major cardiac event on 1-year follow-up. Although nitrates and calcium antagonists are helpful in patients with vasospastic angina, further efforts are needed to identify the molecular alterations responsible for smooth muscle cell hyperreactivity, because a sizeable proportion of patients with vasospastic angina are refractory to standard doses of vasodilators.

It has been observed that fasudil, a specific Rho-kinase inhibitor, reduces the rate of coronary spasm episodes in patients with vasospastic angina. Similarly, further efforts are warranted to unravel the molecular mechanisms responsible for coronary microvascular dysfunction in Takotsubo syndrome and in unstable microvascular angina.

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Keywords: acute coronary syndrome; atherosclerosis; inflammation; microcirculation; plaque erosion; plaque rupture

Pathogenesis of acute coronary syndromes – Crea and others
Physiopathologie et signification clinique de la rupture de plaque

Les modèles expérimentaux d’athérogenèse continuent à apporter leur contribution à la compréhension des mécanismes moléculaires à l’origine du développement de la plaque. Cependant, la transition de la stabilité vers l’instabilité coronaire est moins bien comprise en raison du manque de modèles animaux mimant la pathologie humaine. La survenue brutale d’un syndrome coronaire aigu (SCA) est une indication solide d’une discontinuité de la progression de l’athérothrombose. Les causes de cette discontinuité sont complexes, probablement multiples et encore largement inconnues. La complexité des observations cliniques et post mortem suggère qu’il est improbable qu’une cause unique sera retrouvée pour le phénotype de SCA. Il serait souhaitable d’élaborer une classification pathogénétique du SCA basée sur des descriptifs cliniques simples afin de mieux comprendre les multiples causes d’instabilité coronaire. Dans cet article, nous analysons ces causes dans trois groupes de patients homogènes ayant un tableau clinique similaire : 1) patients avec athérosclérose obstructive et inflammation systémique, 2) patients avec athérosclérose obstructive sans inflammation générale et 3) patients avec altérations fonctionnelles de la circulation coronaire. Une telle classification du SCA offre un cadre pour la compréhension des mécanismes fondamentaux responsables de l’instabilité coronaire plutôt qu’une classification pour un usage clinique immédiat, comme celle fournie par la définition universelle de l’infarctus du myocarde. Cependant, notre classification pathogénétique du SCA basée sur des descriptifs cliniques simples pourrait s’avérer utile dans la recherche de nouveaux algorithmes diagnostiques et de nouvelles cibles thérapeutiques.
The optimal strategy for the management of patients with stable ischemic heart disease (SIHD) has been a matter of considerable debate over the past 2 decades. During this time period, there have been notable technological evolutions in catheter-based revascularization that include the advent of bare-metal and drug-eluting stents, the genesis of more effective antiplatelet therapy, the continued refinement of stent delivery platforms, improving operator experience, and quality improvement initiatives which have led to declining complication rates. As a result, the approach to the management of SIHD has shifted increasingly from an initial pharmacologic strategy to one that embraces an initial percutaneous coronary intervention (PCI) approach. However, such a management paradigm is not fully supported by robust outcomes data, which suggests the need for a critical reappraisal of contemporary clinical practice. In particular, clinical decision making is now better informed because of the results of several important randomized controlled trials that have rigorously compared “hard” clinical end points of death and myocardial infarction (MI) in patients with SIHD who have undergone PCI with contemporary, guideline-directed medical therapy combined with lifestyle intervention.

The 2012 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines on management of stable ischemic heart disease (SIHD) advocate an initial management strategy of intensive medical therapy, reduction in risk factors, and lifestyle modification (best defined as optimal medical therapy [OMT]) rather than an initial percutaneous coronary intervention (PCI) strategy. However, a recent observational study of 467,211 SIHD patients from the National Cardiovascular Data Registry (NCDR) who underwent PCI revealed that only approximately 45% of patients initially received OMT prior to PCI. Importantly, this analysis demonstrated that the percentage of SIHD patients undergoing initial PCI strategy remained similar before and after the COURAGE (Clinical Outcomes Utilizing Revascularization and AGgressive drug Evaluation) study results were published in 2007. These findings are further supported by observational data in SIHD patients from the New York State PCI Registry, where Hannan and colleagues reported that only 11% of patients received routine medical therapy (which was not OMT), while 89% underwent initial PCI. Over the past few decades, PCI has been shown to reduce the incidence of death and myocardial infarction (MI) in patients presenting with acute coronary syndromes (ACS), with the greatest benefit in patients with ST-segment elevation MI (STEMI) and in high-risk non-ST-segment elevation MI (NSTEMI). To date,....
similar clinical benefit on reducing “hard” events has not been demonstrated in randomized controlled trials (RCTs) of patients with SIHD. Over this same period of time, several randomized trials\textsuperscript{9–12} and meta-analyses\textsuperscript{13,14} have yielded remarkably consistent data supporting medical therapy as the optimal initial management strategy in patients with SIHD. However, some more indiscriminate meta-analyses have purported to show benefit of either PCI or myocardial revascularization compared with medical therapy by including either studies of patients with STEMI and/or NSTEMI or combining the results of trials that employed PCI and coronary artery bypass graft (CABG) surgery as part of the revascularization comparison.\textsuperscript{15,16} Such pooling of disparate patient populations and revascularization approaches has created conceptual harm and has done little to clarify the true role of PCI and revascularization on cardiovascular outcomes in patients with SIHD.

**Evidence from contemporary randomized controlled trials and meta-analyses comparing an initial PCI strategy with an initial OMT strategy**

Four recently published randomized studies—the COURAGE trial\textsuperscript{17}, the BARI 2D (Bypass Angioplasty Revascularization Intervention 2 Diabetes) trial,\textsuperscript{18} the JSAP study (Japanese Stable Angina Pectoris),\textsuperscript{19} and the FAME 2 trial (Fractional Flow Reserve versus Angiography for Multivessel Evaluation 2)\textsuperscript{20}—have evaluated an initial strategy of PCI combined with med-

### Table 1. Baseline and angiographic characteristics of major clinical trials comparing initial percutaneous intervention + optimal medical therapy with optimal medical therapy alone in stable ischemic heart disease patients.

<table>
<thead>
<tr>
<th></th>
<th>COURAGE</th>
<th>JSAP</th>
<th>BARI 2D</th>
<th>FAME 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Publication year</strong></td>
<td>2007</td>
<td>2008</td>
<td>2009</td>
<td>2012</td>
</tr>
<tr>
<td><strong>Inclusion criteria</strong></td>
<td>≥70% stenosis of coronary artery + positive stress test or ≥60% stenosis of coronary artery + classic angina</td>
<td>≥60% stenosis of 1- or 2-coronary arteries (except proximal LAD) + positive stress test or exertional angina</td>
<td>T2DM + ≥50% stenosis of coronary artery + positive stress test or T2DM + ≥70% stenosis of coronary artery + classic angina</td>
<td>≥50% stenosis of coronary artery + FFR of ≤0.80%</td>
</tr>
<tr>
<td><strong>Study groups</strong></td>
<td>PCI+OMT vs OMT</td>
<td>PCI+OMT vs OMT</td>
<td>PCI+OMT vs OMT</td>
<td>FFR-guided PCI+OMT vs OMT</td>
</tr>
<tr>
<td>** Patients (N)**</td>
<td>2287</td>
<td>384</td>
<td>2368</td>
<td>888</td>
</tr>
<tr>
<td>** OMT group (N)**</td>
<td>1138</td>
<td>192</td>
<td>1192</td>
<td>441</td>
</tr>
<tr>
<td><strong>Revascularization group (N)</strong></td>
<td>1149</td>
<td>192</td>
<td>1176 (798 PCI, 378 CABG)</td>
<td>447</td>
</tr>
<tr>
<td><strong>Mean age (years)</strong></td>
<td>61</td>
<td>64</td>
<td>62</td>
<td>63</td>
</tr>
<tr>
<td><strong>T2DM</strong></td>
<td>34%</td>
<td>40%</td>
<td>100%</td>
<td>27%</td>
</tr>
<tr>
<td><strong>Previous MI</strong></td>
<td>38%</td>
<td>14%</td>
<td>32%</td>
<td>37%</td>
</tr>
<tr>
<td><strong>Previous revascularization</strong></td>
<td>27%</td>
<td>28%</td>
<td>24%</td>
<td>18%</td>
</tr>
<tr>
<td><strong>PCI</strong></td>
<td>16%</td>
<td>26%</td>
<td>20%</td>
<td>18%</td>
</tr>
<tr>
<td><strong>CABG</strong></td>
<td>11%</td>
<td>2%</td>
<td>6%</td>
<td>Excluded</td>
</tr>
<tr>
<td><strong>Ejection fraction &lt;50%</strong></td>
<td>18%</td>
<td>Excluded</td>
<td>17.5%</td>
<td>17%</td>
</tr>
<tr>
<td><strong>Angina (CCS class)</strong></td>
<td>79% with 0-II</td>
<td>83% with 0-II</td>
<td>61% with 0-II</td>
<td>77% with 0-II</td>
</tr>
<tr>
<td><strong>Angiogram—number of vessels diseased:</strong></td>
<td>31% vs 39% vs 30%</td>
<td>67% vs 33% vs 6%</td>
<td>30% vs 36% vs 31%</td>
<td>Visual: 58% vs 34% vs 8% FFR of ≤0.80%: 76% vs 21% vs 3%</td>
</tr>
<tr>
<td><strong>Multivessel disease (≥2 vessels)</strong></td>
<td>69%</td>
<td>33%</td>
<td>67%</td>
<td>Visual: 42% FFR of ≤0.80%: 24%</td>
</tr>
<tr>
<td><strong>Repeat PCI in PCI+OMT vs PCI in OMT group during follow-up</strong></td>
<td>21.1% vs 32.6%</td>
<td>21.4% vs 36.5%</td>
<td>43.3% vs 42%</td>
<td>3.1% vs 19.5%</td>
</tr>
</tbody>
</table>

**Abbreviations:** BARI 2D, Bypass Angioplasty Revascularization 2 Diabetes; CABG, coronary artery bypass graft; CCS, Canadian Cardiovascular Society; COURAGE, Clinical Outcomes Utilizing Revascularization and Aggressive drug Evaluation; FAME 2, Fractional Flow Reserve versus Angiography for Multivessel Evaluation 2; FFR, fractional flow reserve; JSAP, Japanese Stable Angina Pectoris; LAD, left anterior descending; MI, myocardial infarction; N, number; OMT, optimal medical therapy; PCI, percutaneous coronary intervention; T2DM, type 2 diabetes mellitus.

*Based on data from references 17-20.*
ical therapy compared with medical therapy alone in SIHD patients. In the aggregate, none of these studies have shown any incremental clinical benefit for PCI above and beyond OMT for the reduction in either death or nonfatal MI. The baseline demographics and outcomes of these 4 trials are outlined in Table I and Table II respectively.

The data from these randomized trials are consistent with an earlier meta-analysis by Katritsis and Ioannidis,13 which was published in 2005 prior to the COURAGE trial. That meta-analysis included 11 randomized trials comparing PCI with medical therapy, totaling only 2950 SIHD patients. Importantly, all 11 trials were designed to compare PCI alone against medical therapy, and did not compare PCI plus medical therapy with medical therapy alone. Additionally, the medical therapy employed in these earlier 11 trials antedated the use of disease-modifying therapies that have been commonly employed since 2000, namely statins, inhibitors of the renin-angiotensin system, and thienopyridines. There were no significant differences between the 2 treatment strategies with regard to mortality (odds ratio [OR], 0.94; 95% confidence interval [CI], 0.72-1.24), cardiac death or MI (OR, 1.17; 95% CI, 0.88-1.57), or PCI during follow-up (OR, 1.23; 95% CI, 0.80-1.90). Subsequently, multiple meta-analyses of RCTs have been published that have failed to show any incremental benefit of an initial PCI strategy over an initial OMT strategy in SIHD patients.21-23

In contradistinction, a seriously flawed meta-analysis of 17 randomized trials by Schömig et al15 including 7513 patients was published in 2008 and reported a significant reduction in death (OR, 0.80; 95% CI, 0.64-0.99), and nonsignificant re-

<table>
<thead>
<tr>
<th>COURAGE</th>
<th>JSAP</th>
<th>BARI 2D</th>
<th>FAME 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up</td>
<td>Median – 4.6 years</td>
<td>Mean – 3.3 years</td>
<td>Mean – 5.3 years</td>
</tr>
<tr>
<td>Primary end point (PCI+OMT vs OMT)</td>
<td>Composite of death/nonfatal MI</td>
<td>Death</td>
<td>Death</td>
</tr>
<tr>
<td></td>
<td>19% vs 18.5%; HR, 1.05; 95% CI, 0.87-1.27; P=0.62</td>
<td>2.9% vs 3.9%; HR, 0.865; 95% CI, 0.278-2.604; P=0.794</td>
<td>11.7% vs 12.2%; P=0.97</td>
</tr>
<tr>
<td>ACS</td>
<td>5% vs 11.7%; HR, 0.384; 95% CI, 0.168-0.082; P=0.012</td>
<td></td>
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<tr>
<td>Emergent hospitalization</td>
<td>20.6% vs 31.6%; HR, 0.658; 95% CI, 0.435-0.983; P=0.042</td>
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</tr>
<tr>
<td>Stroke</td>
<td>0.6% vs 1.1%; HR, 0.028; 95% CI, 0.129-8.561; P=0.978</td>
<td></td>
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<tr>
<td>Composite of death/MI/stroke</td>
<td></td>
<td></td>
<td>Composite of death/MI/stroke</td>
</tr>
<tr>
<td>20.0% vs 19.5%; HR, 1.05; 95% CI, 0.87-1.27; P=0.62</td>
<td>21.4% vs 36.5%; P=0.001</td>
<td>22.8% vs 24.1%; P=0.70</td>
<td>0.2% vs 0.7%; HR, 0.33; 95% CI, 0.03-3.17; P=0.31</td>
</tr>
<tr>
<td>Death alone</td>
<td>7.6% vs 8.3%; HR, 0.87; 95% CI, 0.65-1.16; P=0.38</td>
<td>23% vs 21.1%; P=0.15</td>
<td></td>
</tr>
<tr>
<td>Nonfatal MI alone</td>
<td>13.2% vs 12.3%; HR, 1.13; 95% CI, 0.89-1.43; P=0.33</td>
<td></td>
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</tr>
<tr>
<td>Hospitalization for ACS</td>
<td>12.4% vs 11.8%; HR, 1.07; 95% CI, 0.84-1.37; P=0.56</td>
<td></td>
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</tr>
<tr>
<td>Stroke alone</td>
<td>2.1% vs 1.8%; HR, 1.56; 95% CI, 0.80-3.04; P=0.19</td>
<td></td>
<td></td>
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Table II. Outcomes in major clinical trials comparing initial percutaneous coronary intervention + optimal medical therapy with optimal medical therapy alone in stable ischemic heart disease patients.

Abbreviations: ACS, acute coronary syndrome; BARI 2D, Bypass Angioplasty Revascularization 2 Diabetes; CABG, coronary artery bypass graft; CI, confidence interval; COURAGE, Clinical Outcomes Utilizing Revascularization and Aggressive druge Evaluation; FAME 2, Fractional Flow Reserve versus Angiography for Multivessel Evaluation 2; HR, hazard ratio; JSAP, Japanese Stable Angina Pectoris; MI, myocardial infarction; OMT, optimal medical therapy; PCI, percutaneous coronary intervention. Based on data from references 17-20.
ductions in cardiac death (OR, 0.74; 95% CI, 0.51-1.06) and MI (OR, 0.90; 95% CI, 0.66-1.23) in the group with a strategy of initial PCI as compared with medical therapy. The authors concluded that in patients with SIHD, an initial PCI-based strategy might improve long-term survival as compared with an OMT-only strategy. The limitations of the Schömig et al meta-analysis were articulated in an in-depth review and further analysis by Wijeysundera and Ko24 published in 2009 and showed that the original meta-analysis had included 4 trials (2071 patients) that compared the invasive strategy (PCI or CABG) with medical therapy, and 5 trials (1758 patients) that included patients with recent ACS (MI <4 weeks). Therefore, the population analyzed was not homogeneous and is clearly a limitation that would make these findings less generalizable to the SIHD population at large. After excluding the CABG and recent MI studies from the overall Schömig et al data set, there were no residual benefits and no statistically significant difference between PCI and OMT as the initial strategy for managing patients with SIHD (Figure 1).

Another similarly flawed meta-analysis by Jeremias et al16 of 28 studies published from 1977 to 2007 was published in 2009 comparing an initial revascularization strategy (PCI or CABG) with medical therapy. The revascularization modality was PCI in 17 studies, CABG in 6 studies, and either PCI or CABG in 5 remaining studies. There were statistically significant reductions in mortality in the revascularization strategy group (OR, 0.74; 95% CI, 0.63-0.88). A stratified analysis according to revascularization mode revealed both CABG (OR, 0.62; 95% CI, 0.50-0.77) and PCI (OR, 0.82; 95% CI, 0.68-0.99) to be superior to medical therapy with respect to mortality.

Selected abbreviations and acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>ACC</td>
<td>American College of Cardiology</td>
</tr>
<tr>
<td>ACS</td>
<td>acute coronary syndrome</td>
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<tr>
<td>AHA</td>
<td>American Heart Association</td>
</tr>
<tr>
<td>BARI 2D</td>
<td>Bypass Angioplasty Revascularization Intervention 2 Diabetes</td>
</tr>
<tr>
<td>CABG</td>
<td>coronary artery bypass graft</td>
</tr>
<tr>
<td>CAD</td>
<td>coronary artery disease</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>COURAGE</td>
<td>Clinical Outcomes Utilizing Revascularization and Aggressive druG Evaluation</td>
</tr>
<tr>
<td>ESC</td>
<td>European Society of Cardiology</td>
</tr>
<tr>
<td>FAME</td>
<td>Fractional Flow Reserve versus Angiography for Multivessel Evaluation</td>
</tr>
<tr>
<td>FFR</td>
<td>fractional flow reserve</td>
</tr>
<tr>
<td>ISCHEMIA</td>
<td>International Study of Comparative Health Effectiveness with Medical and Invasive Approaches</td>
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<tr>
<td>JSAP</td>
<td>Japanese Stable Angina Pectoris</td>
</tr>
<tr>
<td>MI</td>
<td>myocardial infarction</td>
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<tr>
<td>NCDR</td>
<td>National Cardiovascular Data Registry</td>
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<tr>
<td>NSTE-MI</td>
<td>non-ST-segment elevation myocardial infarction</td>
</tr>
<tr>
<td>OMT</td>
<td>optimal medical therapy</td>
</tr>
<tr>
<td>OR</td>
<td>odds ratio</td>
</tr>
<tr>
<td>PCI</td>
<td>percutaneous coronary intervention</td>
</tr>
<tr>
<td>RCT</td>
<td>randomized controlled trial</td>
</tr>
<tr>
<td>SIHD</td>
<td>stable ischemic heart disease</td>
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<tr>
<td>STEMI</td>
<td>ST-segment elevation myocardial infarction</td>
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</table>

Figure 1. Summary odds ratios of meta-analyses of the impact on mortality: percutaneous coronary intervention versus medical therapy in patients with stable coronary artery disease.

Abbreviations: CABG, coronary artery bypass graft; CI, confidence interval; COURAGE, Clinical Outcomes Utilizing Revascularization and Aggressive druG Evaluation; MI, myocardial infarction; OR, odds ratio; PCI, percutaneous coronary intervention.

surgery versus medical therapy in an earlier era of rather primitive medical therapy (aspirin, β-blockers, and nitrates only). Finally, the statistical significance for superiority in the PCI arm of this meta-analysis (upper CI of 0.99) nearly crossed the line of unity. All of the above limitations should render the findings drawn from this meta-analysis as inconclusive and not generalizable to the SIHD population.

A subsequent meta-analysis by Wijeysundera and Ko25 of 14 studies including 7818 patients was published in 2010 and demonstrated that an initial PCI strategy was associated with overall greater freedom from angina compared with medical therapy (OR, 1.69; 95% CI, 1.24-2.30). The authors also stratified the trials by year of enrollment and found that the 3 trials prior to 1994 and the 6 trials between 1995 and 1999 showed significant freedom from angina in the PCI strategy compared with medical therapy. On the contrary, the 5 trials after year 2000 showed no difference in angina relief between PCI and medical therapy groups (Figure 2).25 That finding was large-

ly attributable to the use of robust evidence-based medical therapy attenuating the effect of PCI on angina relief in contemporary trials, which likely “leveled the playing field” in effectively reducing angina in the intensively treated patients.

These conflicting results from various meta-analyses very likely reflect the selection bias of pooling scientific data from noncontemporaneous studies differing in study design and duration, raising the concern about comparing “apples and oranges.”26

**What constitutes OMT?**

As previously described, while there has been sustained technological evolution of PCI since its inception, similar impressive advancements in both our understanding of the pathophysiology of coronary artery disease (CAD) and newer therapeutic agents have led to the development of an effective “disease-modifying” pharmacologic therapy with proven survival benefits.1 These agents include antiplatelet agents, statins, β-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), and aldosterone antagonists. Additionally, agents that provide symptomatic relief of angina and ameliorate ischemia are likewise important components of OMT and include β-blockers, calcium channel blockers, nitrates, inhibitors of late inward sodium flux such as ranolazine, the selective I f current inhibitor ivabradine, the potassium channel agonist nicorandil, and the metabolic agent trimetazidine.1,27

The 2012 ACC/AHA1 and the 2013 European Society of Cardiology (ESC)27 guidelines recommend intensive lifestyle intervention combined with aggressive pharmacologic therapy for SIHD, the goal of which is to reduce cardiovascular morbidity and mortality, as well as the burden of symptoms and ischemia in these patients. The guidelines strongly emphasize that these lifestyle changes should include cessation of cigarette smoking, maintenance of a healthy weight, regular physical activity (a minimum of 30-45 minutes 4-5 times/week), and adoption of a healthy diet (a diet low in saturated fat, cholesterol, and trans-fat; high in fresh fruits, whole grains, and vegetables; and with reduced sodium intake). In the aggregate, the combination of aggressive risk factor modification and intensive medical therapy is referred to as OMT.

**Trials favoring an initial strategy of OMT in SIHD patients**

The COURAGE trial17 randomized 2287 patients with SIHD to an initial strategy of PCI plus OMT versus OMT alone. Patients were included in the study if they had evidence of significant
coronary artery stenosis on coronary angiography and objective evidence of ischemia or classic anginal symptoms. This was at least an intermediate-risk population. During a median follow-up of 4.6 years, the primary end point of all-cause mortality or nonfatal MI occurred in 211 patients in the PCI plus OMT group and 202 patients in the OMT group (19% vs 18.5%; P=0.62) (Figure 3). There were no significant differences between the groups in regard to the prespecified secondary end point of composite of death, MI, and stroke, and of hospitalization for unstable angina with negative biomarkers alone as shown in Table II.

In examining the COURAGE data further, in terms of symptom relief, PCI plus OMT resulted in a more rapid symptomatic relief from angina. However, after 4.6 years of follow-up, reported symptoms were no longer statistically different. Overall, these findings support the hypothesis that there was no clear benefit of initial PCI strategy over initial OMT alone in terms of mortality, nonfatal MI, or cumulative major cardiovascular events in SIHD patients and no long-term difference in angina relief, which has often been touted as the rationale for defaulting to an initial PCI strategy.

Subsequently, the BARI 2D trial randomized 2368 patients with type 2 diabetes mellitus and SIHD to initial revascularization groups, either in the form of PCI or CABG, in combination with OMT versus initial OMT alone. Patients with type 2 diabetes mellitus and evidence of documented coronary artery stenosis on coronary angiography with positive stress imaging or classic angina were included. The primary end point of all-cause mortality was not statistically significantly different, with a 5-year survival of 88.3% in the revascularization arm versus 87.8% in the OMT arm (P=0.97) (Figure 4A). The secondary end point of composite of death, MI, or stroke (major cardiovascular events) was also not statistically different between revascularization and OMT-alone groups (Figure 4B). When analyzed separately based on the type of revascularization, patients who underwent PCI plus OMT showed no significant difference versus OMT alone in terms of total mortality and major cardiovascular events (Figure 4C), which is also consistent with the findings of COURAGE.

In the CABG subgroup of BARI 2D, overall mortality was similar to that in the OMT-alone group, but the CABG group had significantly fewer cardiovascular events (Figure 4D), which was driven primarily by the reduction in number of nonfatal MIs in the CABG arm. Overall, these findings demonstrate that in diabetic patients with SIHD, an initial strategy of PCI in combination with OMT did not offer any additional, or incremental, benefits compared with OMT alone in terms of all-cause mortality or the composite major cardiovascular events. However, CABG appears to reduce the rate of nonfatal MI when compared with OMT alone in diabetic patients who exhibited more extensive CAD, generally those with 3-vessel CAD. The strategy of CABG for revascularization may be beneficial for diabetic patients with more extensive CAD.

Trials designed to show benefit of an initial PCI strategy in SIHD patients

The JSAP study randomized 384 low-risk SIHD patients to an initial strategy of PCI plus OMT versus an initial strategy of OMT alone. Patients with evidence of documented coronary stenosis in 1 or 2 vessels on coronary angiography, other than the proximal left anterior descending artery, with a positive stress test or exertional angina were included. The primary end point of cumulative death rate was not significantly differ-
In summary, these findings of the JSAP study demonstrated that in low-risk patients with SIHD, an initial strategy with PCI in combination with OMT does not offer additional benefits to OMT alone in terms of all-cause mortality or nonfatal MI. However, initial PCI plus OMT resulted in lower rates of unstable angina, emergency hospitalization, and elective repeat revascularization. Furthermore, an initial strategy with PCI appeared to provide more symptomatic angina relief at 3.3 years of follow-up compared with an initial strategy of OMT alone. Compared with contemporary randomized trials such as COURAGE and BARI 2D, it is important to recognize that JSAP included minimally symptomatic, low-risk CAD patients, who were treated with less intensive routine medical therapy in both groups at baseline and over the follow-up period, but did not receive OMT.

To evaluate the efficacy of fractional flow reserve (FFR)-guided PCI, the FAME trial (Fractional Flow Reserve versus Angiography for Multivessel Evaluation) randomized 1005 patients with multivessel CAD to conventional angiographic-guided PCI or FFR-guided PCI (PCI performed only if FFR was \( <0.80 \)). The composite of death, nonfatal MI, and repeat revascularization was significantly lower at 1 and 2 years in the FFR-guided PCI group. Unlike COURAGE, BARI 2D, and JSAP trials, the original FAME trial did not have a medical therapy comparator arm. Thus, while the study results added to the body of literature on utility of FFR to guide PCI, it did not address the key scientific issue of which initial strategy, either OMT or FFR-guided PCI, was optimal in the management of SIHD.

![Figure 4. Major clinical end points in the BARI 2D trial.](image-url)
SIHD patients. Therefore, the FAME 2 trial\(^2\) was undertaken in order to address the lack of an OMT comparator in the original FAME trial, and in this more recent study, 888 patients with SIHD were randomized to an initial strategy of FFR-guided PCI plus OMT versus an initial strategy of OMT alone. Only patients who had evidence of coronary artery stenosis on coronary angiography with an FFR $\leq 0.80$ were included, while those with an FFR $>0.80$ were followed in a registry and treated medically. The Data and Safety Monitoring Board halted the recruitment prematurely owing to significant differences in the primary end points between the 2 groups. After a mean follow-up of merely 7 months, the primary end point of the composite of all-cause mortality, nonfatal MI, or unplanned hospitalization leading to urgent revascularization was significantly lower in the group with FFR-guided PCI plus OMT as compared with the initial OMT-alone group (4.3% vs 12.7%; \(P<0.001\)) (Figure 5A–D). This difference was primarily driven by significantly lower rates of urgent revascularization in the initial PCI-plus-OMT group than in the initial OMT-alone group. There were no significant differences between the groups in the prespecified secondary end point of death or nonfatal MI. The proportion of patients with angina class II to IV was considerably higher among patients randomized to initial PCI plus OMT than among those randomized to initial OMT alone. Importantly, this was likely a very low–risk group, in that there were very few cardiac events observed after 12 months (see section on limitations of FAME 2 below). The results of the FAME 2

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**Figure 5. Major clinical end points in FAME 2.**

Abbreviations: CI, confidence interval; FAME 2, Fractional Flow Reserve versus Angiography for Multivessel Evaluation 2; PCI, percutaneous coronary intervention.

study were comparable to the JSAP study in that the initial strategy of PCI plus OMT did not reduce the rates of death or nonfatal MI in SIHD patients, but seemed to provide more symptomatic anginal relief.

**Limitations of FAME 2**

FAME 2 has received significant criticism primarily because the demonstrated benefit of PCI over OMT was limited to the “soft” end point of urgent revascularization without affecting the incidence of the more meaningful “hard” end points (ie, cardiovascular mortality or nonfatal MI). Overall, there were very few “hard” events with only 4 total deaths and 29 MIs. In the OMT-alone group, there were 3 deaths and 14 MIs compared with the PCI-plus-OMT group which had 1 death and 15 MIs. There was only 1 cardiac death in each group. After 12 months, there were just 2 MIs, both in the PCI-plus-OMT group, and no deaths in either group. The trial was designed to enroll 1632 patients, with a projected 2-year follow-up period; however, it was terminated at a mean follow-up of 7 months after enrolling only 54% of planned participants because of a highly significant treatment difference, a finding driven solely by a difference in the end point of urgent revascularization. More than half of the unplanned revascularizations (52%) were performed solely on the basis of reported clinical symptoms without supporting evidence of positive cardiac biomarkers or electrocardiographic evidence of ischemia. In the context of a nonblinded trial, there is clearly a concern that decisions regarding interventions during follow-up may have been biased by the knowledge of the previous treatment assignment. Biologically, the follow-up period was also far too short (average 7 months) for coronary restenosis to emerge. Therefore, a longer follow-up might have narrowed the difference in the rates of unplanned revascularization between the groups. Furthermore, the study population in FAME 2, when compared with COURAGE, did not appear to be at particularly high risk (as evidenced by multivessel disease 24% vs 69%, respectively). Finally, while fewer than 80 patients had 12 months of follow-up, the benefit of PCI in improving class II to IV angina symptoms was not significant beyond 6 months.

In summary, while FAME 2 did show that an FFR-guided PCI strategy resulted in a lower rate of unplanned revascularization as compared with medical therapy alone, the notable limitations of the trial as highlighted above makes it difficult to justify or generalize the more widespread use of an FFR-guided revascularization approach in the management of SIHD patients.

**Future directions**

The ISCHEMIA trial (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches; Clinical Trials.gov, NCT 01471522), funded by the US National Institutes of Health, is currently under way. ISCHEMIA is designed and powered to evaluate the long-term superiority of revascularization of choice combined with OMT versus a strategy with OMT alone with respect to cardiovascular death or MI (composite primary end point) in patients with stable CAD and moderate-to-severe myocardial ischemia as assessed by noninvasive stress imaging studies (myocardial perfusion imaging, stress echocardiography, or magnetic resonance imaging). The ISCHEMIA trial is projected to enroll 8000 patients from among 400 enrolling sites worldwide, with a planned average follow-up period of 4 years. In conclusion, based on the best available data from multiple randomized trials, it would appear both reasonable and justifiable to defer an initial strategy of PCI in favor of an adequate empirical trial of OMT as a strategy that can be advocated for the majority of patients with SIHD and Canadian Cardiovascular Society (CCS) class I or II anginal symptoms. In SIHD patients with refractory and/or worsening symptoms, despite OMT (ie, “failed medical therapy”), or those with high-risk criteria on noninvasive testing, such as inducible ischemia involving a moderate or large territory of myocardium, an initial revascularization strategy with PCI could be considered appropriate until further data from the ISCHEMIA trial informs our clinical practice of how best to treat these patients.

**References**


8. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous throm-


**Keywords:** coronary artery disease; myocardial ischemia; optimal medical therapy; revascularization; stable ischemic heart disease

ÉVOLUTION DES CONCEPTS DANS LA DÉFINITION DES STRATÉGIES OPTIMALES POUR LA PRISE EN CHARGE DES PATIENTS CORONAIENS STABLES

Ces 20 dernières années, la stratégie optimale pour la prise en charge des patients coronariens stables a fait l’objet de nombreux débats. Cette période a connu de grandes avancées technologiques dans la revascularisation par cathéter, avec l’avénement des stents métalliques nus et actifs, au développement de traitements antiplaquettaires plus efficaces, à l’amélioration constante des plateformes de stents libérant les principes actifs, à l’expérience croissante des intervenants et aux initiatives d’amélioration de qualité. Ces avancées ont permis une diminution des taux de complications. Ceci explique que la prise en charge de la maladie coronaire stable ait de plus en plus évolué de la stratégie pharmacologique initiale vers l’intervention coronaire percutanée (ICP) de première intention. Cependant, aucun résultat solide ne vient conforter complètement ce modèle de prise en charge, ce qui suggère la nécessité d’une réévaluation critique de la pratique clinique actuelle. Ainsi, la prise de décision clinique est d’ores et déjà mieux informée grâce aux résultats de plusieurs importantes études contrôlées randomisées ayant comparé rigoureusement des critères cliniques « durs » de décès et d’infarctus du myocarde (IDM) chez des patients coronariens stables ayant subi une ICP, à un traitement médical moderne selon les recommandations, associé à des interventions sur le style de vie.
The practice of percutaneous revascularization for treatment of coronary artery disease (CAD) has significantly evolved over time as a consequence of numerous technical and pharmacological advances in the field. These advances have resulted in improved outcomes and the ability to treat sicker patients with more complex coronary morphology. Marked changes over recent decades in patient characteristics, procedural pharmacotherapy, and secondary prevention have transformed the immediate and longer-term outcomes achievable with percutaneous revascularization, especially in patients presenting with acute coronary syndromes. However, in patients with stable CAD, both the indications for and benefit (and hence appropriateness) of stented angioplasty applied as a default therapy based on angiographic anatomical guidance have been challenged. With the advent of pressure-derived fractional flow reserve, an invasive vessel-specific measurement of the extent to which epicardial stenosis reduces normal vessel conductance, it has become clear that many seemingly severe stenoses on angiography actually fail to be of hemodynamic significance. Moreover, the combined use of anatomical and functional guidance for stent targeting in revascularization has been shown to produce results that are symptomatically equivalent and prognostically superior to those involving targeting driven only by angiographic anatomical guidance. This article reviews recent evidence derived from ischemia-guided stent implantation trials demonstrating the benefits of appropriately targeted stent implantation on symptoms, prognosis, and health economics.

Medicographia. 2014;36:55-62 (see French abstract on page 62)
Coronary stent implantation: an established therapeutic modality and the dominant mode of myocardial revascularization

Major technical and procedural advances have transformed coronary balloon dilatation as initially performed by Grützig into a safe, reliable, efficacious, predictable, and durable therapy involving implantation of drug-eluting coronary stents. At the same time, procedures have remained minimally invasive and patient friendly. Patients presenting with acute myocardial infarction or other unstable coronary syndromes are best treated with early percutaneous intervention. Patients with complex lesions who were traditionally referred for bypass surgery have progressively more often been treated with stents, including those with complex bifurcation stenosis, chronic coronary occlusion, left main stenosis, or multiple diseased vessels. Currently, the main limitation of stented angioplasty no longer relates to technical feasibility, but rather its ability to address extensive and diffuse CAD such as is seen in patients with diabetes, with worse outcomes reported in this context than with surgery. There seems to be a limit to the number of stent implants, i.e., the epicardial vessel length that is covered by metal, beyond which outcomes start to degrade. With the emergence of fully bioresorbable scaffolds, this last frontier may be crossed in the near future (scaffolds are fully biodegradable drug-eluting stents that disappear within a few years after implantation). Today, however, the anatomical extent and severity of CAD is the frontier, and the borders are defined by the upper tertile of the SYNTAX score (SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery). This score qualifies the anatomical extent of the disease using coronary angiography, and identifies patients with extensive disease who should be recommended for bypass surgery rather than implantation of multiple permanent stents.

Percutaneous revascularization has greatly benefited from advances in adjunctive medical therapies. Antiplatelet and antiplatelet drugs have reduced periprocedural and in-hospital stent thrombosis rates to 1%-3%. Late stent thrombosis rates have decreased with use of the newer-generation drug-eluting stents to the extent that long-term dual antiplatelet therapy (beyond 6 months) may no longer be required. As a result, antiplatelet drug prescriptions and secondary prevention regimes are now driven by the disease indications, rather than the device.

In this context, percutaneous revascularization using stented angioplasty has become the first-choice mode of therapy in many clinical and anatomical situations. Because of all of the aforementioned, it comes as no surprise that stents represent the dominant mode of revascularization, constantly exceeding the annual number of bypass procedures performed since the late 1990s.

Evidence and evolving practice patterns

The evidence base for stent implantation in patients with stable CAD is derived from randomized clinical trials, large propensity-matched observational registries, and their meta-analyses. Only 2 studies have shown a mortality benefit, both of which included patients with recent myocardial infarction. In one of these studies by Jeremias et al, after excluding patients with myocardial infarction from their meta-analysis, the authors still reported evidence for reduced mortality (hazard ratio, 0.82; confidence interval, 0.68-0.99).

Data consistently show an improvement in symptoms with use of stent implantation, but for the most part, no reduction in hard outcomes events: no benefit of percutaneous revascularization over medical treatment with respect to mortality, nonfatal periprocedural myocardial infarction, or the need for repeat revascularization.

Because of the significant advances in both revascularization and medical therapies over the last 2 decades, many of the reported clinical trials have limited relevance in today’s clinical practice. The randomized trial COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive druG Evaluation), which was discussed earlier in this issue (see preceding article), did demonstrate that major adverse cardiac outcome events after 4.6 years of best contemporary medical therapy were not improved by performance of angioplasty as the initial strategy. It was concluded from COURAGE that percutaneous revascularization should be restricted to patients who remain symptomatic after medical therapy, a conclusion that can hardly be drawn from the study design, as only patients with known coronary anatomy were eventually considered for randomization in the study. As is usually the case in randomized clinical trials, only a small proportion of eligible patients were included in the trial, which thus limits the possibility of extrapolation of the results to all patients seen in routine clinical practice, especially those whose coronary anatomy is not known.

Nevertheless, the impact of COURAGE on interventional practice has been very significant, with fewer stented angioplasty procedures being performed in stable CAD patients than pre-
vidually. Procedures in catheterization laboratories now involve an increasing proportion of patients with acute CAD in whom the benefits of revascularization by stent implantation have been proven. Of note, identification of the offending stenosis in such patients is mostly unambiguous. Moreover, the remaining indications for stent implantation in stable CAD patients are now carefully scrutinized and sometimes declared inappropriate, especially when they are primarily—let alone exclusively—based on technical feasibility.

**Indications for revascularization in patients with stable CAD**

The guidelines on myocardial revascularization that were issued in 2010 by both the European Society of Cardiology and the European Association for Cardiothoracic Surgery were the first to propose a stepwise decision process whereby the appropriateness of revascularization is addressed first, followed only secondly by the technical discussion about the relative merits of bypass versus stent implantation. Revascularization can be justified on symptomatic grounds, with persistent limiting symptoms of angina or angina equivalent despite optimal medical care. Prognostic indications, which are most often present in conjunction with symptoms, but can even be present in asymptomatic patients, are justified in anatomical subsets associated with proven large territories of stress-inducible ischemia. Significant left main or proximal left anterior descending stenosis, especially in the presence of multivessel disease, represents an anatomical situation that involves large areas of myocardium at risk, and thus has the potential to show an improved outcome after revascularization.

These recommendations underscore the prognostic importance of ischemic burden and demonstrable ischemia (death, myocardial infarction, acute coronary syndromes). While there is no prognostic benefit of revascularization in symptomatic patients with little evidence of ischemia, patients with 10% or more of the myocardium at jeopardy will enjoy a lower risk of death or infarction after revascularization, as shown from large functional imaging studies. A small nuclear substudy of COURAGE has confirmed these findings in the era of contemporary medical treatment, showing lower event rates with reduced mass of ischemic myocardium under treatment, be it revascularization or medical therapy only. The evidence for a lack of benefit in the absence of demonstrable ischemia is perhaps even stronger and has been augmented over the last decade by studies incorporating ischemia detection into the decision-making process regarding whether to revascularize or to defer (see Table I).

**Anatomy-guided versus ischemia-guided revascularization**

With the extension of the indications for percutaneous revascularization, decisions regarding whether to revascularize or not have increasingly been made solely on the basis of angiography findings; namely, the presence of seemingly "significant" coronary narrowing. Indeed, in many patients who reach the catheterization laboratory, a functional evaluation has not been undertaken. This can be for one, or several, of the following reasons: (i) with more complex anatomy, noninvasive functional testing often only identifies the most severe abnormalities; (ii) in the presence of multivessel disease, the ability of all imaging techniques to qualify the significance of individual stenoses on a "per vessel" basis remains far from perfect; (iii) in patients with prior myocardial infarction, diagnosis of ischemia in other territories is difficult; and (iv) ad hoc revascularization (meaning that stented angioplasty is performed immediately after diagnostic angiography) is convenient, but increases the likelihood that stent implantation will be performed in the absence of functional testing.

<table>
<thead>
<tr>
<th>Year</th>
<th>Study</th>
<th>Source</th>
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<tbody>
<tr>
<td>1997</td>
<td>ACIP trial</td>
<td>Davies16</td>
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<tr>
<td>2003</td>
<td>Nuclear imaging studies</td>
<td>Hachamovitch14</td>
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<tr>
<td>2008</td>
<td>Nuclear substudy COURAGE</td>
<td>Hachamovitch14</td>
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<tr>
<td>2009</td>
<td>Substudy of BARI 2D</td>
<td>Shaw19</td>
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<tr>
<td>2012</td>
<td>FAME 2 randomized trial</td>
<td>De Bruyne20</td>
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**Evidence for benefit of revascularization if moderate/large ischemia**

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<th>Year</th>
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<td>2005</td>
<td>Besançon randomized trial</td>
<td>Legay22</td>
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<tr>
<td>2007</td>
<td>DEFER randomized trial</td>
<td>Bech16, Pijs17</td>
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<tr>
<td>2010</td>
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**Evidence for lack of benefit of revascularization in the absence of ischemia**

<table>
<thead>
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<td>1997</td>
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<tr>
<td>2012</td>
<td>FAME 2 randomized trial</td>
<td>De Bruyne20</td>
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</table>

*Table I. Studies assessing the benefit of percutaneous revascularization in the presence or absence of ischemia.*

**Abbreviations:** ACIP, Asymptomatic Cardiac Ischemia Pilot; BARI 2D, Bypass Angioplasty Revascularization Investigation 2 Diabetes; COURAGE, Clinical Outcomes Utilizing Revascularization and Aggressive drug Evaluation; DEFER, not an acronym; FAME, Fractional flow reserve versus Angiography for Multi-vessel Evaluation.

These (and other) limitations of noninvasive functional testing are real and explain why precathe-terization examinations often fall short of providing the interventional cardiologist with clear directions as to where to act. This situation is unfortunate, but explains why invasive doctors often have had no choice but to react to images, applying the so-called oculostenotic reflex. This is indeed unfortunate, because angiography is notoriously known to not provide a reliable estimate of stenosis severity. Whether or not ischemia will be inducible downstream of a coronary stenosis depends on stenosis severity and geometry, as well as several other factors. Among these factors, the most important are the mass and viability of downstream myocardium, and above all, the effectiveness of collateral circulation, which can hardly be assessed by angiography.
Stable coronary artery disease: an evolving picture

With the validation and clinical application of pressure-derived fractional flow reserve (FFR) measurement, it became obvious that many seemingly severe stenoses on angiography actually fail to be of hemodynamic significance (Figure 1). FFR is an invasive, vessel-specific measurement of the extent to which epicardial stenosis reduces normal vessel conductance. The measurement is based on the simultaneous registration of proximal and distal intracoronary pressures during maximal hyperemia. Thus, FFR identifies the likelihood that epicardial vessel conductance is sufficiently reduced that it will cause downstream myocardial ischemia during increased demand. As a corollary, mechanical treatment by percutaneous coronary intervention or coronary artery bypass grafting (CABG) becomes increasingly likely to augment maximal flow, and hence eliminate symptoms and improve prognosis, when applied to stenoses with more severely reduced FFR.

Prospective studies have indeed shown that angiographic guidance in the absence of functional testing, be it noninvasive or FFR-based, results in about 30% overtreatment and 20% undertreatment, which equates to inadequate stent placement in as many as 50% of patients. The clinical implications of this are massive. Studies have shown that stented angioplasty could be safely deferred whenever stenoses were not limiting maximal flow capacity. When using stents to dilate stenoses in patients with preserved FFR, patients showed no symptom improvement over medically-treated patients. Actually, stent implantation in the absence of ischemia should not be of any benefit and could even be harmful. Although infrequent, as with any invasive procedure, there remains the potential for complications with stent implantation. Table II shows the results of FAME (Fractional flow reserve versus Angiography for Multivessel Evaluation) I, in which revascularization strategies based on angiography alone are compared with those using angiography and fractional flow reserve.

The implications for health technology assessment are equally striking (Figure 2). Revascularization based solely on angiographic results regarding any beneficial effects of revascularization. Understandably, the benefit of the procedure will be restricted to patients with extensive ischemia. Indeed, if up to half of stents are inadequately targeted in angiography-driven trials, sample size calculations will be skewed, side effects will be magnified, and net outcome trial results will be flawed.

### Table II

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>496</th>
<th>509</th>
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<tbody>
<tr>
<td>No. of lesions/patient</td>
<td>2.7±0.9</td>
<td>0.34</td>
</tr>
<tr>
<td>No. of stents/patient</td>
<td>2.7±1.2</td>
<td>0.001</td>
</tr>
<tr>
<td>Total DES</td>
<td>1359</td>
<td>980</td>
</tr>
<tr>
<td>At 1 year:</td>
<td></td>
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<tr>
<td>No event/no angina</td>
<td>68%</td>
<td>0.07</td>
</tr>
<tr>
<td>Death/infarction</td>
<td>12.9%</td>
<td>0.02</td>
</tr>
<tr>
<td>Repeat PCI/CABG</td>
<td>12.7%</td>
<td>0.30</td>
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</table>

From a clinical trial perspective, randomized allocation to percutaneous stent implantation in patients with coronary lesions that do not cause ischemia will confound and dilute trial results regarding any beneficial effects of revascularization. Understandingly, the benefit of the procedure will be restricted to patients with extensive ischemia. Indeed, if up to half of stents are inadequately targeted in angiography-driven trials, sample size calculations will be skewed, side effects will be magnified, and net outcome trial results will be flawed.

**Figure 1. Understanding (in)appropriate use of percutaneous coronary intervention.**

Each data point refers to a coronary stenosis that was evaluated both with quantitative coronary angiography (an objective method to calculate the stenosis severity from the angiogram) and fractional flow reserve (FFR). The horizontal axis shows the percentage diameter stenosis, with a 50% stenosis as the threshold for significance. The vertical axis shows the corresponding FFR value, with the abnormality threshold at 0.80. The individual data clusters in 4 quadrants: Quadrants I and III correspond to consistent evaluation between anatomy and physiology. Less than 50% diameter stenosis with preserved FFR (quadrant I): PCI inappropriate. More than 50% diameter stenosis with abnormal FFR (quadrant III): PCI appropriate. However, many seemingly severe stenoses by angiography do not alter FFR (quadrant II): PCI questionable. Other seemingly nonobstructive stenoses do nevertheless alter FFR (quadrant IV): PCI deferral is inappropriate.

**Abbreviations:** FFR, fractional flow reserve; PCI, percutaneous coronary intervention.

Rethinking stent implantation for stable CAD patients

Targeting revascularization procedures to stenoses proven to cause ischemia results in a totally new paradigm that challenges previously accepted standards. With this knowledge at hand, the FAME 2 trial was designed to show the superiority of stented angioplasty over optimal medical therapy in patients with ischemia documented by FFR who were then randomized 1:1 to medical treatment only or medical treatment plus stent implantation. The final report of the study is awaited, but initial outcome data were presented after study enrolment was stopped prematurely due to an excess of urgent hospitalization events requiring unplanned revascularization in the group assigned to optimal medical care only. Because enrolment was halted prematurely, it is unlikely that the trial hypothesis will be met when the primary outcome data at 24 months become available (the planned release is during the first quarter of 2014). However, unplanned hospitalization events requiring urgent revascularization—as opposed to comfort interventions—were associated with an increased rate of death or myocardial infarction between 8 and 215 days (Figure 3, page 60). These data indicate that a default strategy of medical therapy alone is inappropriately denying 11.1% of patients revascularization, while also exposing them to significant risk (strongly positive interaction). In addition, 8.6% of patients randomized to optimal medical care remained symptomatic and required elective revascularization on average as soon as 6 months after inclusion. Whether the remaining 80.3% of the subset of ischemic patients randomized to optimal medical care who were appropriately spared from upfront revascularization (either for prognostic or symptomatic indications) can be identified a priori has yet to be evaluated.

Future impact of new stenting paradigms: disruption of existing practices and outcomes

Implementation of combined functional-anatomical guidance for coronary stenting and myocardial revascularization will be disruptive of current practice in several respects. The results of FAME 1 showed an inherent weakness in revascularization guidance based primarily on the coronary angiogram. Anatomy is misleading, and treatment decisions based on this type of guidance can be flawed: too many stents are deployed and are inappropriately targeted to stenoses that do not need intervention, while too few stents are deployed and are inappropriately denied treatment. FAME 1 thus demonstrates that more stents do not mean more care. Specifically, 2 major challenges will have to be managed. First, if investigators are reluctant to include and randomize patients with a large ischemic burden or severe coronary disease, only lower-risk patient subsets will be included and event rates will be low, and this trial will neither be conclusive nor generalizable to practice. Conversely, if high-risk patients are indeed included and randomized, an excess of unplanned revascularization procedures will occur in the medical treatment arm and safety considerations may emerge, potentially challenging the continued inclusion of such patients. For both FAME and ISCHEMIA, data safety monitoring committees play a critical role in monitoring trial execution and progress.

The ongoing trial ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) is attempting to resolve the remaining uncertainty and address some of the limitations of FAME 2. The primary end point in ISCHEMIA will be death or nonfatal myocardial infarction, and the trial will be powered accordingly. Unlike the FAME trials, the functional evaluation will evaluate noninvasive testing and imaging techniques. Based on the recent experience with FAME 2, it may turn out to be a challenge to successfully complete this randomized trial. Specifically, 2 major challenges have to be managed. First, if investigators are reluctant to include and randomize patients with a large ischemic burden or severe coronary disease, only lower-risk patient subsets will be included and event rates will be low, and this trial will neither be conclusive nor generalizable to practice. Conversely, if high-risk patients are indeed included and randomized, an excess of unplanned revascularization procedures will occur in the medical treatment arm and safety considerations may emerge, potentially challenging the continued inclusion of such patients. For both FAME and ISCHEMIA, data safety monitoring committees play a critical role in monitoring trial execution and progress.
The results of FAME 2 illustrated the limitations of applying in clinical practice the results of previously reported trials that concluded inadequately that revascularization has no prognostic value.23 Between a strategy that uses too many stents upfront and a strategy of default initial medical therapy with no initial use of stents at all, optimal care likely resides in the middle, whereby stents are used where needed in the presence of proven ischemia. Such a strategy requires combined functional-anatomical guidance, and has been demonstrated to be disruptive of current practice through provision of superior outcomes while saving resources.31

The implications are far reaching. By replacing the previous gold standard based on anatomy with a combined functional-anatomical strategy, the definitions of disease and disease subsets are changing. The extent and severity of coronary disease is being reclassified; from triple-vessel to double-vessel or single-vessel disease, from double-vessel to single-vessel disease, or sometimes to disease that is called “nonsignificant” and thus amenable to optimal medical care only. Risk stratification based on anatomy (the SYNTAX score) changes accordingly when the “functional” SYNTAX score is applied.34 Likewise, demands on the completeness of revascularization procedures are being...
It is tempting to speculate that the results of trials such as SYNTAX, which compared multiple-vessel stenting with bypass surgery, would have been different had stenting indications not been based solely on anatomy (Figure 4). The trial failed to meet its primary noninferiority end point, with the significant difference at 5 years in favor of bypass surgery being primarily driven by stent failure, mostly causing an excess in the need for repeat revascularization. The average number of implanted stents was 4.6±2.3 per patient, the average stent length was 86.1 mm, and 48% of patients received 5 stents or more.

References
7. Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS); European Association for Percutaneous Cardiovascular Interventions (EAPci); Wijns W, Kolh P, Danchin N, et al. Guidelines on myocardial revascularization. Eur Heart J. 2010;31:2501-2555.
De nombreuses avancées techniques et pharmacologiques ont significativement fait évoluer la revascularisation percutanée dans le traitement de la maladie coronaire (MC). Ces progrès ont permis d’améliorer les résultats et de traiter des patients avec des atteintes plus graves et des présentations coronaires anatomiques plus complexes. Ces dernières décennies, des changements importants des caractéristiques des patients, des modalités de pharmacothérapie et de la prévention secondaire ont entraîné une amélioration des résultats immédiats et à long terme réalisables avec la revascularisation percutanée, en particulier chez les patients présentant un syndrome coronaire aigu. Cependant, chez les patients atteints de MC stable, les indications et les bénéfices (et donc la pertinence) de l’angioplastie par stent comme traitement par défaut guidée par les constatations anatomiques fournies par la coronarographie, sont remis en cause. De nombreuses sténoses qui semblent sévères à l’angiographie n’ont en fait pas de retentissement hémodynamique fonctionnel significatif comme le montre la réserve de flux fractionnel (FFR) dérivée de la pression, qui mesure de façon invasive et spécifique la réduction de la conductance vasculaire due à la sténose épicardique. De plus, l’utilisation combinée d’un guidage fonctionnel et anatomique en vue de l’implantation d’un stent pour revascularisation a montré des résultats identiques sur le plan des symptômes et supérieurs sur le plan du pronostic à ceux obtenus seulement par coronarographie anatomique. Cet article analyse les données récentes, issues d’études de revascularisation par stent pour ischémie, des bénéfices de cette technique correctement ciblée en termes de symptômes, pronostic et économies de santé.
Elevated heart rate seems to play a role in the development and progression of coronary atherosclerosis, and numerous studies have shown an association between increased heart rate and cardiovascular mortality. In line with this concept, recent clinical data show that selective heart rate reduction is beneficial for the secondary prevention of coronary events. The underlying explanations for these associations are still unclear. Furthermore, whether elevated heart rate is simply a compensatory response to existing cardiac pathology or has a direct causal role in the manifestation of cardiac events remains to be investigated. The mechanisms that may account for the pathophysiological effects of high heart rate on plaque morphology include endothelial dysfunction, vascular inflammation, as well as effects on vascular wall mechanics. Experimental data have highlighted the antiatherogenic potential of selective heart rate lowering and provide a strong rationale for its assessment in the clinical setting.

Medicographia. 2014;36:63-72 (see French abstract on page 72)
The prognostic value of resting heart rate in acute cardiovascular events

Most epidemiological studies in this area have demonstrated an association between elevated heart rate and cardiovascular mortality, while the relationship between heart rate and acute coronary events or sudden cardiac death is less well understood. Several studies provide strong support for heart rate as an independent and strong risk predictor of sudden cardiac death in various populations (Figure 1),6-8 and it remains a risk predictor after adjustment for potential confounding variables.2-6,15 The prognostic value of heart rate in time heart rate does not predict events (Figure 2).10,11 The differential effects of heart rate on cardiovascular outcomes may indicate that potential confounders, eg, increased sympathetic nervous system activity, play a greater role or have a higher prevalence in populations that experience plaque rupture compared with patients with stable atherosclerotic disease. However, differences may also have arisen in studies simply due to a lack of statistical power or because of the competitive risk phenomenon.

A subanalysis of the placebo arm of the prospective BEAUTIFUL (morBidity-mortality EvaLUaTion of the I<sub>1</sub> inhibitor ivabradine in patients with coronary artery disease [CAD] and left ventricular dysfunction) showed that heart rates of ≥70 beats per minute (bpm) were associated with more admissions to hospital for myocardial infarction (MI) than heart rates of <70 bpm (46% increase, P=0.0066).9 Numerous other studies have shown that increasing heart rate is associated with increased risk for MI12,20 or left ventricular remodeling following MI.24 Clinical studies have shown that episodes of myocardial ischemia in patients with stable CAD are triggered by an increase in heart rate,25,26 and ischemic activity and heart rate have been demonstrated to show similar circadian variations.27 Results of a study by Heidland and colleagues point toward a possible mechanism accounting for the association between heart rate and adverse outcomes. They showed a positive association between plaque disruption and a mean heart rate above 80 bpm in patients who underwent 2 coronary angiograms within 6 months, indicating that hemodynamic forces might have a critical role in the process of plaque destabilization.12

**Elevated heart rate–pathophysiology**

**Causative factor or epiphenomenon?**

One question that remains to be answered is the following: does a high heart rate signal a more “damaged” heart than a low heart rate? An elevated heart rate is often found to correlate with traditional cardiovascular risk factors such as hypertension, dyslipidemia, diabetes, and obesity.28 Not surprisingly, the correlation between cardiovascular disease (CVD) and high resting heart rate seems to be more pronounced in pa-

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**Figure 1.** Adjusted hazard ratios of heart rate for sudden cardiac death in different studies and populations.

Only hazard ratios that have been adjusted for traditional cardiovascular risk factors are shown. Data are presented as hazard ratio and 95% confidence interval. **Abbreviations:** bpm, beats per minute; CAD, coronary artery disease; NSTEMI, non-ST elevation myocardial infarction; RHR, resting heart rate.

### Characteristics of study population

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>P value for interaction</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy males, RHR &gt;75 bpm</td>
<td>5713</td>
<td>&lt;0.001</td>
<td>Jouven²</td>
</tr>
<tr>
<td>Healthy males, mean RHR</td>
<td>7746</td>
<td>=0.03</td>
<td>Jouven³</td>
</tr>
<tr>
<td>Healthy males, RHR &gt;90 bpm</td>
<td>7735</td>
<td>&lt;0.01</td>
<td>Shaper⁴</td>
</tr>
<tr>
<td>CAD, RHR &gt;80 bpm</td>
<td>3708</td>
<td>&lt;0.01</td>
<td>Williams⁵</td>
</tr>
<tr>
<td>Hospital admission for NSTEMI, RHR &gt;80 bpm</td>
<td>9461</td>
<td>&lt;0.0001</td>
<td>Boersma⁶</td>
</tr>
</tbody>
</table>

**Adjusted hazard ratio for sudden cardiac death**
tients with these risk factors.\textsuperscript{28} Increased resting heart rate is also associated with poor exercise capacity, which is itself a strong predictor of mortality.\textsuperscript{29}

Nonetheless, in most epidemiological studies, when adjustments were made for traditional risk factors, heart rate still independently predicted risk for cardiovascular mortality. However, this is not always the case for risk prediction of acute coronary events. Indeed, clinical confounders appear to attenuate the association between increased heart rate and MI.\textsuperscript{15} Thus, it seems likely that an elevated heart rate is causative in progression of atherosclerosis, but the relationship between heart rate and ACS or sudden cardiac death seems to be more difficult to explain. So, does heart rate mediate the deleterious effects of sympathetic hyperactivity? It is known that patients with ACS have impaired autonomic function with sympathetic hyperactivity,\textsuperscript{30} and that increased sympathetic nerve activity is associated with an adverse outcome following MI.\textsuperscript{31} This observation is supported by experimental studies in monkeys in which psychosocial stress induced endothelial injury and subsequent atherosclerotic lesion formation in coronary arteries.\textsuperscript{32} Sympathetic hyperactivity is detected not only in patients with MI, hypertension, or cerebrovascular disease, but also in patients with obesity, metabolic syndrome, and diabetes mellitus.\textsuperscript{33,34} Experimental studies have shown that stimulation of the sympathetic nervous system can cause myocardial apoptosis as well as sudden cardiac death.\textsuperscript{35} In summary, it is currently difficult to strictly separate the effects of sympathetic neuroendocrine regulation and elevated heart rate on acute cardiac events. Experimental studies with pure heart rate–lowering drugs will certainly help to establish whether fast heart rate is a marker or a mediator of sympathetic overactivity in the induction of risk.

\textbf{Heart rate and plaque progression}

Clinical data have shown that heart rate is directly associated with progression of atherosclerosis.\textsuperscript{1} Increasing evidence indicates that shear stress might be the link between heart rate and atherosclerosis. A fast heart rate increases the magnitude and frequency of repetitive tensile stress on the arterial wall by increasing mean blood pressure.\textsuperscript{36} By shortening the diastolic phase of the cardiac cycle, the exposure of the endothelium to the low and oscillatory systolic shear stress is prolonged, while protective diastolic shear stress is reduced.\textsuperscript{37,38} In addition, high heart rate intensifies the pulsatile motion of the heart and, consequently, the frequency of intense phasic changes in torsion that also induce significant shear stress to the coronary vessels.\textsuperscript{39}

Shear stress has been shown to affect endothelial cell gene and protein expression profiles, to alter vascular smooth muscle cell proliferation, and to increase oxidative stress. Con-

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\begin{tabular}{|l|c|c|c|}
\hline
Characteristics of study population & N & $P$ value for interaction & Reference \\
\hline
Healthy males, mean RHR & 7746 & NS & Jouven\textsuperscript{3} \\
Recent CVI, RHR >70 bpm & 18,980 & =0.029 & Fox\textsuperscript{7} \\
Healthy males, RHR >90 bpm & 7735 & NS & Shaper\textsuperscript{4} \\
Postmenopausal women, RHR >76 bpm & 129,135 & =0.001 & Hsia\textsuperscript{8} \\
CAD and systolic dysfunction, RHR >70 bpm & 5438 & =0.0066 & Fox\textsuperscript{9} \\
CAD and hypertension, no prior MI & 15,138 & NS & Kolloch\textsuperscript{16} \\
CAD and hypertension, prior MI & 7054 & NS & Kolloch\textsuperscript{16} \\
CAD, RHR >83 bpm & 24,913 & NS & Diaz\textsuperscript{17} \\
CAD, mean RHR & 9580 & NS & Ho\textsuperscript{18} \\
Vascular disease, mean RHR & 1054 & NS & Bemelmans\textsuperscript{10} \\
Elderly subjects >65 years & 7147 & NS & Legeai\textsuperscript{20} \\
Hospital admission for NSTEMI, RHR >130 bpm & 135,164 & =0.027 & Bangalore\textsuperscript{21} \\
Hypertension, nighttime HR per 10 bpm increase & 7600 & =0.0069 & Palatini\textsuperscript{13} \\
Mixed population, mean nighttime HR & 6928 & <0.01 & Hansen\textsuperscript{11} \\
\hline
\end{tabular}
\caption{Adjusted hazard ratios of heart rate for acute coronary events in different studies and populations. Only hazard ratios that have been adjusted for traditional cardiovascular risk factors are included. Data are presented as hazard ratio and 95% confidence interval. Abbreviations: bpm, beats per minute; CAD, coronary artery disease; CVI, cerebrovascular incident; HR, heart rate; MI, myocardial infarction; NSTEMI, non-ST elevation myocardial infarction; RHR, resting heart rate.}
\end{table}

\textbf{Figure 2.} Adjusted hazard ratios of heart rate for acute coronary events in different studies and populations.
tributing mechanisms include induction of growth-promoting factors, matrix-degrading enzymes, cytokines, and adhesion and prothrombotic molecules and chemottractants, as well as increased expression of proatherogenic genes (e.g., endothelin-1). In turn, nitric oxide activity is reduced and uptake of oxidative enzymes (reduced nicotinamide adenine dinucleotide phosphate, xanthine oxidase) and low-density lipoprotein are increased. Indeed, it has been shown that an experimental increase in heart rate in rats significantly increases cardiac oxidative stress. The reverse was shown in apolipoprotein E knockout (apoE–/–) mice treated with the heart rate–lowering drug ivabradine.

In humans, microinflammatory markers have been found to increase progressively with heart rate, and systemic inflammation and endothelial dysfunction have been shown to be associated with an increased heart rate in the elderly. Following shear stress, changes in endothelial submembranous cytoskeleton might result in higher endothelial permeability, facilitating migration of inflammatory cells and infiltration of inflammatory markers (Figure 3). Experimental studies have shown that heart rate reduction with ivabradine prevents or reverses endothelial dysfunction associated with dyslipidemia, and this was associated with >40% and >70% reductions in atherosclerotic plaque size. Accordingly, heart rate has been shown to be a strong predictor of microalbuminuria prevalence, a marker of generalized endothelial injury that correlates with end organ damage.

In vascular smooth muscle cells, shear stress induces upregulation of extracellular matrix protein growth factors, matrix metalloproteinases, and osteogenic markers, resulting in the

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**Figure 3.** Heart rate and vulnerable plaque development. Schematic diagram of hypothetical effects of heart rate on plaque destabilization, involving mechanisms contributing to necrotic core enlargement (blue panels) and fibrous cap thinning (red panels). Elevated heart rate is thought to cause coronary endothelial dysfunction and inflammation of the vascular wall by lowering shear stress and increasing cyclical wall stresses. Dysfunctional endothelium is characterized by secretion of growth factors, cytokines, adhesion molecules, an increase in reactive oxygen species and depletion of nitric oxide due to decreased activity of endothelial nitric oxide synthase (eNOS). This promotes monocyte recruitment, platelet aggregation, migration of inflammatory cells and secretion of inflammatory molecules. eNOS is known to depress sympathetic activity, which in turn has been shown to induce apoptosis of vascular cells.

**Abbreviations:** EC, endothelial cell; ICAM-1, intercellular adhesion molecule 1; IL, interleukin; MCP-1, monocyte chemoattractant protein-1; MMP, matrix metalloproteinase; NO, nitric oxide; oxLDL, oxidized low-density lipoprotein; PDGF, platelet-derived growth factor; ROS, reactive oxygen species; TF, tissue factor; TNF-α, tumor necrosis factor α; VCAM-1, vascular cell adhesion protein 1; VSMC, vascular smooth muscle cell.
breakdown of elastin and an increased vascular rigidity (Figure 4).\textsuperscript{14} Two recent studies have shown that arterial stiffness is an independent predictor of cardiovascular events and mortality in healthy individuals and patients with CAD.\textsuperscript{57,58} Experimental studies in rats have shown that tachycardia promotes marked reductions in arterial compliance and distensibility in coronary and femoral arteries.\textsuperscript{59,60} Consistent with this finding, treatment with ivabradine improved aortic compliance in rats and apoE\textsuperscript{−/−} mice.\textsuperscript{61} In vitro data indicate that stretching of human smooth muscle cells enhances the release of angiotensin II in a frequency-dependent manner, thereby stimulating production of collagen in the vascular wall.\textsuperscript{62} In hypertensive and normotensive humans, a heart rate of >80 bpm is associated with increased arterial rigidity of large peripheral arteries,\textsuperscript{63,64} and an elevated heart rate during sleep is significantly associated with increased arterial rigidity in patients with chronic kidney disease.\textsuperscript{65} Whether this effect also occurs in coronary arteries remains unclear; however, it seems reasonable that an increase in the number of stretch cycles experienced by large elastic arteries would accelerate deterioration of arterial wall components such as elastin fibers, leading to increased arterial stiffness (Figure 4).

\textbf{Heart rate and plaque rupture}

Clinical data suggest that elevation of heart rate is associated with an increased risk of ACS and sudden cardiac death.\textsuperscript{2-4,8,9,15} This is supported by findings from an angiographic study in humans, as well as ex vivo data demonstrating that disruption of vascular plaques is augmented with increasing heart rates.\textsuperscript{12,13} A retrospective analysis in patients with obstructive CAD revealed that patients with heart rates of <50 bpm develop collateral vessels more often than patients with heart rates of >60 bpm.\textsuperscript{66} This notion was supported by experimental data in rats showing that pharmacological induction of bradycar-
dia with alinidine enhanced vascularity and coronary reserve and preserved the function of surviving myocardium in the postinfarcted heart by upregulation of vascular endothelial growth factor (Figures 3 and 4).

In the presence of a well-developed collateral system, the occlusion of an epicardial vessel results in reduced tissue necrosis during an MI and may thus result in lower mortality. In addition, elevated heart rates are associated with disproportionate decreases in the duration of diastole. As a consequence, coronary perfusion and myocardial oxygen supply are reduced, leading to induction or exacerbation of myocardial ischemia, which may result in or contribute to ACS. Finally, increasing the heart rate of patients with CAD by atrial pacing causes paradoxical coronary vasoconstriction, thereby further compromising coronary perfusion and myocardial performance (Figure 4).

As discussed, there is evidence that heart rate is a stronger predictor of sudden cardiac death than of nonfatal coronary events. This could be explained by the fact that in experimental models of myocardial ischemia, an increase in baseline heart rate not only triggered ischemic episodes, but also lowered the threshold for both supraventricular and ventricular arrhythmias (Figure 4). In humans, high resting heart rate was independently associated with ventricular arrhythmia, the major cause of sudden cardiac death. Accordingly, in mice, ivabradine reduced lethal arrhythmias associated with dilated cardiomyopathy.

The probability of plaque rupture depends on the stability of the fibrous cap covering the plaque shoulder, the size of the lipid core, as well as the mechanical stress imposed upon it (Figure 3). An increased heart rate could induce mechanical stress on the vessel wall, as the latter depends on the duration and frequency of cardiac cycles. Mechanical stresses affecting plaque morphology include circumferential wall stress, repetitive tensile stress, and low systolic shear stress, but also flexion and mechanical stresses induced by cardiac motion, which have been consistently linked to the development of vulnerable plaques and an increased risk of plaque disruption (Figure 3). In rupture-prone areas, cyclic bending (which increases with heart rate) has been identified by computational magnetic resonance imaging–based models as a relevant stressor that provokes plaque disruption. Modified endothelial shear stress and pulsatile wall stress profiles lead, via mechanoreceptors, to secretion of growth factors, cytokines, and adhesion molecules, and an increase in reactive oxygen species and depletion of endothelial nitric oxide synthase (eNOS). This promotes monocyte recruitment, platelet aggregation, migration of inflammatory cells, and secretion of inflammatory molecules, which may promote weakening of the fibrous cap (Figure 4). In addition, eNOS is known to depress sympathetic activity, likely by increasing parasympathetic tone, and eNOS depletion may therefore account for the sympathetic drive and the increase in norepinephrine observed with increasing heart rate (Figures 3 and 4).

Clinical implications

Clinical outcome benefits associated with heart rate reduction

A meta-analysis of randomized clinical trials strongly suggests that the beneficial effects of β-blockers and nondihydropyridine calcium antagonists are proportionally related to the reduction in resting heart rate. Pharmacological intervention with the current inhibitor ivabradine exerted antianti-ischemic effects in patients with CAD or microvascular angina in randomized clinical trials, and appeared to significantly reduce coronary event rates in the subgroup of patients with a heart rate of ≥70 bpm in BEAUTIFUL. Ivabradine has no direct effects on the vascular system other than to reduce heart rate, and therefore opens up promising opportunities for the study of the effects of exclusive heart rate lowering on the progression of atherosclerosis as well as plaque rupture.

The 2012 European Society of Cardiology guidelines for heart failure treatment recommend ivabradine for patients in sinus rhythm with an ejection fraction of ≤35%, a heart rate remaining at ≥70 bpm, and persisting symptoms despite β-blocker treatment (class Ila recommendation) or in those with β-blocker intolerance (class IIb recommendation).

Risk assessment and optimal target heart rate

There seems to be a continuous increase in risk with heart rate values of >60 bpm. In most clinical trials, a heart rate of >70 bpm has been chosen to identify patients at risk. Nevertheless, cutoff values to have shown a prognostic value for cardiovascular outcomes have varied widely between trials and have ranged between 70 bpm and 83 bpm in CAD patients, with lowest mortality rates seen at between 50 bpm and 59 bpm. The frequency of ambulatory ischemic episodes in patients with CAD has been reported to be twice as high for patients with a mean heart rate of >80 bpm as those with a heart rate of <70 bpm. In summary, defining precisely when a heart rate should be considered “elevated” is challenging; however, prospective studies including BEAUTIFUL show convincing evidence that a heart rate of >70 bpm is deleterious in patients with stable CAD. This would imply that heart rates that are presently considered to be normal may well be detrimental to prognosis. Although American guidelines recommend aiming for a heart rate of between 55 bpm and 60 bpm for the prevention of angina, current guidelines give no recommendation as to a target heart rate for improvement of cardiovascular prognosis. Resting heart rate is included in prognostic models for ACS such as the Global Registry of Acute Coronary Events (GRACE) risk prediction score, the Cooper Clinic risk index for overall mortality, and the recent dynamic Thrombolysis in Myocardial Infarction (TIMI) risk score for ST-segment elevation myocardial infarction. By contrast, heart rate is not included in the European SCORE project (Systematic COrony Risk Evaluation) or the Copenhagen Risk Score.
The predictive value of ambulatory heart rate is still being debated, since both an increased heart rate and reduced heart rate variability seem to be independently associated with increased mortality. Thus, it may be useful to assess heart rate using 24-hour Holter recordings. This is emphasized by the results of 2 recent studies that demonstrated that ambulatory nighttime heart rate as assessed by 24-hour recording added to the risk stratification for cardiovascular events. Measuring nighttime heart rate seems to be an attractive alternative to outpatient heart rate monitoring for assessing the risk of these devastating events. However, to assess the risk of all-cause and cardiovascular mortality, heart rate measured with a conventional electrocardiogram seems to carry similar predictive power to 24-hour mean heart rate obtained from Holter recordings. The 2012 European guidelines on CVD prevention in clinical practice recommend measuring resting heart rate after a 5-minute rest, which should form part of the routine outpatient physical examination when assessing cardiovascular risk.

Heart rate recovery 3 minutes after exercise was recently identified as an additional measure to predict cardiovascular mortality. Indeed, in a recent study, a heart rate recovery of <46 bpm identified patients at risk for all-cause mortality and diabetes. Moreover, the heart rate profile during exercise and recovery seems to be a predictor of sudden death. Observational studies have demonstrated that heart rate measured during follow-up after MI provides more prognostic information than heart rate measured at baseline. Prospective evidence determining whether modulation of measurement settings can reduce or increase the prognostic value of heart rate in different patient populations is needed.

Conclusions and future directions

Taken together, the evidence shows that an elevated heart rate is positively associated with cardiovascular mortality, cardiovascular events, and sudden cardiac death. This association is strong and is independent of other risk factors for cardiovascular mortality and sudden cardiac death, while the association between heart rate and acute cardiovascular events could be dependent on other risk factors and measurement time points.

There is a complex interaction between various biomechanical and hemodynamic stresses mediating the effect of heart rate on plaque vulnerability and the risk of rupture. Coronary imaging techniques such as intravascular ultrasonography, virtual histology, computer-assisted quantitative coronary angiography analysis, and optical coherence tomography may help in understanding the complex interactions that are involved in heart rate–induced changes in the morphological appearance of atherosclerotic vulnerable plaques and luminal stenoses. These imaging modalities are being used in MODIFY (reducing elevated heart rate in patients with Multiple Organ Dysfunction Syndrome [MODS] by Ivabradine), which is evaluating the effects of ivabradine on coronary atherosclerosis.

It has been demonstrated that despite frequent use of β-blockers, stable CAD patients often have a resting heart rate of >70 bpm, which has been shown to be associated with worse overall health status and more frequent angina and ischaemia. Thus, further heart rate lowering is possible in many patients with CAD. Whether selective heart rate lowering improves cardiovascular outcomes will be tested in the large-scale SIGNIFY trial (Study assessing the morbidity-mortality benefit of the I inhibitor ivabradine in patients with coronary artery disease) in patients with CAD, no heart failure, and a resting heart rate of ≥70 bpm in sinus rhythm. Finally, the worldwide CLARIFY registry (Prospective observational Longitudinal Registry of patients with stable coronary artery disease) will help obtain data on long-term prognosis in outpatients with elevated heart rate and stable CAD.

Acknowledgments. Dr Tardif holds the Canada Research Chair in translational and personalized medicine and the Université de Montréal endowed research chair in atherosclerosis. In the interest of brevity, we have referenced other reviews whenever possible and apologize to the authors of the numerous original papers that were not explicitly cited.
STABLE CORONARY ARTERY DISEASE: AN EVOLVING PICTURE


Vlachopoulos C, Assimakopoulou P, Stefanidou C. Prediction of cardiovascular events


88. Kosters R, Kanshin J, Meinertz T. Treatment of stable angina pectoris by ibavara-
Une fréquence cardiaque élevée semble jouer un rôle dans le développement et la progression de l’athérosclérose coronaire. En effet, un grand nombre d’études montrent une association entre une fréquence cardiaque élevée et la mortalité cardio-vasculaire. C’est ainsi que des données cliniques récentes montrent qu’une réduction sélective de la fréquence cardiaque est bénéfique pour la prévention secondaire des événements coronaires. L’explication sous-jacente de ces associations n’est pas encore très claire. Il faut de plus rechercher si une élévation de la fréquence cardiaque est simplement une réponse compensatoire à une pathologie cardiaque existante ou si elle a un rôle causal direct dans la manifestation des événements cardiaques. La dysfonction endothéliale, l’inflammation vasculaire et les effets sur la mécanique de la paroi vasculaire sont des mécanismes pouvant expliquer les effets physiopathologiques d’une fréquence cardiaque élevée sur la morphologie de la plaque. Des données expérimentales soulignent le potentiel antiathérogène d’un abaissement sélectif de la fréquence cardiaque et fournissent un argument solide pour son évaluation dans un cadre clinique.

**Keywords:** acute coronary syndrome; heart rate; ivabradine; plaque rupture
This fellowship is designed to foster the work of young researchers in the cardiovascular field

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to Prof Peter Ferdinandy
peter.ferdinandy@pharmahungary.com
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- This initiative follows the Servier SNS Research Grant, awarded from 2003 through 2007. The winners were Markus Schlaich, Krzysztof Narkiewicz, and Gino Seravalle.
- The winners of the Servier Research Grant in Hypertension were Konstantin Kotliar (Munich, Germany) in 2011 and Stefano Masi (London, UK) in 2013.
- The **Servier Research Grant in Hypertension** is limited to PhDs or MDs under 45 years of age on July 1 in the year of the award.

Next deadline for applications: **January 30, 2015**
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E-mail: giuseppe.mancia@unimib.it
More information is available at [www.esonline.org](http://www.esonline.org) and on the Servier Web site: [www.servier.com](http://www.servier.com)

- Servier, with the European Society for Microcirculation (ESM), is offering a research award: the **Servier Award in Microcirculation**.
- A €4,000 grant is offered every 2 years for an outstanding clinical or basic research publication in the fields of microcirculation and vascular biology. The call for applications is advertised on the ESM Web site and by related societies and journals.
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- The 2013 Servier Award in Microcirculation was presented to Helge Wijg and Agnes Schröder who received the prize during the 27th European Society for Microcirculation Congress in Birmingham (UK), July 21-26, 2013.
- Applications should be submitted no later than September 2014, and will be reviewed by a committee composed of 8 members including officers of the ESM. Scientists under 40 years of age on January 31 in the year of the award may apply.

Next deadline for applications: **September 30, 2014**
Applications should be sent to the ESM general secretary Prof Akos Koller: akos.koller@aok.pte.hu
More information is available on the ESM Web site: [www.esmicrocirculation.eu](http://www.esmicrocirculation.eu) and on the Servier Web site: [www.servier.com](http://www.servier.com)

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- Candidates less than 45 years old and belonging to a National Society affiliated with the UIP may apply.

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**THE QUESTION**

Coronary artery disease (CAD) is still highly prevalent worldwide, and stable angina pectoris is one of its most common presentations. However, many stable CAD patients have inducible ischemia—mostly without weekly or more frequent symptoms of angina. Even in the absence of angina, inducible ischemia is associated with an increased risk of recurrent CAD events. Should therapy in stable CAD patients be guided by ischemia or by angina; moreover, should those without angina receive anti-ischemic therapy?

**Should stable CAD patients without angina receive anti-ischemic therapy?**

1. M. Abdel Hamid, *Egypt*
2. S. Al-Saif, *Saudi Arabia*
3. E. Atalar, *Turkey*
4. L. M. Cesar, *Brazil*
5. G. H. Choo, *Malaysia*
6. X. Garcia-Moll, *Spain*
7. Y. Karpov, *Russia*
8. U. Laufs, *Germany*
9. N. Mewton, *France*
10. T. Q. Nguyen, *Vietnam*
11. A. N. Parkhomenko, *Ukraine*
12. R. Seabra-Gomes, *Portugal*
13. S. Y. Tan, *Singapore*
14. C. J. Vaughan, *Ireland*
15. P. H. Zelveian, *Armenia*
Coronary artery disease (CAD) may be asymptomatic or may cause angina, myocardial infarction (MI), heart failure, arrhythmias, or sudden death. Silent ischemia is typically defined as objective evidence of myocardial ischemia in patients without symptoms related to that ischemia. In fact, asymptomatic (or silent) ST-segment depression during ambulatory electrocardiogram (ECG) monitoring occurs more often than symptomatic ST-segment depression in patients with CAD. In a study in patients with medically managed CAD, the likelihood of death or MI during 7 years of follow-up was similar for patients with asymptomatic ST-segment depression and those with symptomatic ST-segment depression with exercise. Silent ischemia during ambulatory ECG monitoring was a more powerful predictor of mortality than exercise duration, age, previous MI, hypertension, diabetes, or smoking history.

Should therapy in patients with stable CAD be guided by angina symptoms or by ischemia? The goals of CAD treatment are to reduce the risk of disease progression and prevent acute coronary syndromes (ACS) and cardiovascular death, as well as to relieve symptoms and improve quality of life in patients with stable CAD. Silent myocardial ischemia is a major component of the total ischemic burden for patients with CAD. Management of CAD should aim to reduce or eliminate myocardial ischemia by risk factor modification, aggressive medical therapy, and, if appropriate, myocardial revascularization.

Optimal management of CAD includes the following: (i) Appropriate lifestyle modification; ie, no smoking, a healthy diet, weight control, and regular exercise. (ii) Detection and treatment of diseases and conditions that increase the risk of atherosclerosis, in particular, hypertension, diabetes, and hypercholesterolemia. (iii) Statin therapy. Regardless of low-density lipoprotein (LDL) cholesterol levels, all patients with CAD should be taking a statin, as this has been shown to reduce disease progression. In addition, statins have significant mortality benefits and multiple trials have demonstrated a reduction in ACS with their use, even in CAD patients with normal LDL levels. Statins have anti-inflammatory properties and plaque stabilization abilities that are independent of their LDL-lowering effect. (iv) Additional preventive therapy with aspirin, other anti-thrombotic agents, angiotensin-converting enzyme inhibitors, and β-blockers in patients with known atherosclerosis. Every patient with documented CAD should be taking antiplatelet therapy, usually in the form of aspirin, for the prevention of ACS. Low-dose aspirin (75 mg to 150 mg) has been shown to be equally effective as medium-dose aspirin (162 mg to 325 mg), with less gastrointestinal bleeding complications. In addition, clopidogrel, prasugrel, and ticagrelor reduce recurrent events in the first year after an ACS. β-Blockers seem to be the most effective agents; according to the results of ASIST (Atenolol Silent Ischemia Study), they reduce the incidence, frequency, duration, and severity of silent ischemia. Treatment with atenolol 100 mg/day reduced daily ischemia, as well as the risk of future adverse cardiac events at 1 year. The National Institute for Health and Care Excellence guidelines recommend offering either a β-blocker or calcium channel blocker as first-line treatment for stable angina, with the choice of drug depending on comorbidities, contraindications, and the person’s preference. (v) Symptomatic treatment with nitrates, β-blockers, calcium channel blockers, and other antianginal drugs. (vi) Revascularization by percutaneous coronary intervention or coronary artery bypass grafting in selected patients. Revascularization exerts favorable effects on symptoms, quality of life, exercise capacity, and survival, particularly in those with extensive CAD and documented moderate-to-severe ischemia.

Additionally, future research is warranted to study the effect of newer medical therapies such as ivabradine and ranolazine, or selected use of revascularization in those patients with persistent silent ischemia despite use of optimal current-era medical therapy.
Relief of angina pectoris (AP) is one of the goals of therapy in patients with stable coronary artery disease (CAD). Patients with previously asymptomatic CAD, or those with CAD whose symptoms were previously stable, can develop acute coronary syndromes (ACS) that often require hospitalization. In 2008, an estimated 935 000 individuals in the United States had a myocardial infarction (MI), and 195 000 experienced a silent first MI. Many more were hospitalized for unstable angina and for evaluation and treatment of AP. In the same year, the prevalence of AP in the United States was 9 million, and each year it is estimated that half a million people develop new AP. Even when these patients do not require hospital admission, they often experience worsening of their quality of life. Prevention of factors that can trigger or worsen myocardial ischemia is therefore an essential aspect of the long-term management of patients. This must be combined with prevention of the progression of underlying atherosclerosis as well as resultant MI, left ventricular dysfunction, heart failure, and sudden cardiac death. Maintenance or restoration of activity levels, functional capacity, and quality of life in a manner that is satisfactory to the patient is another essential goal of therapy. This requires elimination of symptoms of ischemia during daily activities. To achieve this, optimal medical therapy is utilized, in addition to revascularization procedures in selected patients. The presence or absence of symptoms of AP did not influence the cumulative 5-year outcome among diabetic patients in the BARI 2D study (Bypass Angioplasty Revascularization Investigation in type 2 Diabetes study). Patients without AP should therefore receive evidence-based therapies in the same manner as other symptomatic patients. Patients with evidence of an ischemic burden of 5%-10% derive benefit from revascularization. Patients with coronary lesions with a fractional flow reserve value of less than 0.8 also derive benefit from percutaneous coronary intervention. All patients benefit from antiplatelet therapy with daily low-dose aspirin. Control of patients’ heart rate to below 70 beats per minute is effective in controlling ischemia. This is best achieved using β-blockers, and by adding ivabradine when necessary. In addition, patients require control of established risk factors in the following manner: (i) achievement of low-density lipoprotein cholesterol levels of less than 70 mg/dL through lifestyle changes that include dietary measures, as well as the use of statins; (ii) complete cessation of smoking, including no exposure to passive smoking; (iii) achievement of a blood pressure level of 130/80 mm Hg through lifestyle changes and the use of drugs, including an angiotensin-converting enzyme inhibitor; (iv) control of diabetes by achievement of a glycated hemoglobin level of 7% with no hypoglycemia; and (v) maintenance of an adequate level of physical activity. Therefore, in answering the question as to whether or not stable CAD patients without angina should receive anti-ischemic therapy, the answer is a definite yes.

References
Silent myocardial ischemia is the most common manifestation of coronary artery disease (CAD). Silent ischemia can be detected by electrocardiogram (ECG), through ambulatory ECG monitoring in daily life, or with an exercise test or pharmacological stress test. Nearly half of stable CAD patients have silent ischemia.

Patients with silent ischemia have similar degrees of myocardial ischemia to patients with symptomatic ischemia, with an increased risk of coronary events and mortality. The precise reason for the adverse prognosis associated with silent ischemia is not known. Possibly, repeated episodes of ischemia, whether symptomatic or silent, cause irreversible myocardial changes related to development of fibrotic myocardium, which would act as an ideal substrate for development of life-threatening arrhythmias or heart failure. Patients with silent ischemia commonly receive less medical or interventional therapy than those with symptomatic ischemia, and there is little evidence about the optimal management strategy for this specific group. The 2 basic therapeutic goals in CAD patients are relief of angina and ischemia, and prevention of myocardial infarction, left ventricular dysfunction, and death.

Nitrates, β-blockers, calcium antagonists, and trimetazidine, alone and in combination, were previously shown to reduce the incidence, frequency, duration, and severity of symptomatic ischemia, but also silent ischemia. High heart rate (HR) is detrimental for myocardial ischemia and is an independent predictor of morbidity and mortality in CAD patients; thus, ivabradine, a new HR-reducing agent, has been shown to decrease myocardial ischemia and improve cardiac outcomes. Combinations of anti-ischemic agents have been found to be superior to individual agents in reducing ischemia. Reduction in silent ischemic episodes has also been documented with aspirin, statins, and angiotensin-converting enzyme inhibitors.

Recent studies have also shown that anti-ischemic drug therapy reduces cardiac events in patients with asymptomatic ischemia. ACIP (Asymptomatic Cardiac Ischemia Pilot study) found no difference in event rates between the angina- and ischemia-guided medical treatment groups, but revascularization was better than medical therapy in reducing silent ischemic episodes. Furthermore, ACIP showed a trend toward decreased cardiovascular event rates in those patients with a greater reduction in the number of ischemic episodes with medical treatment, particularly after revascularization. Several studies have suggested that the presence and extent of ischemia is a major predictor of response to revascularization. One suggested that the benefits of revascularization were limited to patients with inducible ischemia of ≥10% of the left ventricular myocardium.

COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) demonstrated similar outcomes in those CAD patients receiving revascularization and optimal medical therapy (OMT) to those receiving OMT alone. However, subgroup analyses from COURAGE showed worse outcomes in cases of complex CAD and a high extent of inducible ischemia, and early revascularization plus OMT was better than OMT alone in reducing ischemic outcomes in these high-risk patients. Based on this evidence, the cornerstone of therapeutic decision-making in stable CAD seems to be the extent of objective ischemia on stress imaging.

Elimination of ischemia in CAD patients is key to improve prognosis. Management of stable CAD patients should be based not only on ischemic symptoms, but also the presence and extent of documented myocardial ischemia. Ambulatory ECG may help detect silent ischemia, but pharmacological stress tests give more information about the presence, severity, and extent of ischemia. Those with more extensive ischemia probably benefit more from revascularization plus OMT than OMT alone. There is no ideal therapy for silent ischemia. Such patients should be treated as symptomatic and receive anti-ischemic therapy and revascularization as needed.

References

We must answer 2 questions: (i) Does ischemia provoke death and/or events? (ii) Will treatment of ischemia prevent these end points, and if so, which treatment type(s) will be of influence?

Since the results of CASS (Coronary Artery Surgery Study), we have known that ischemia elicited on exercise testing is prognostic for death and myocardial infarction (MI). The same has been shown in studies involving ambulatory electrocardiogram (ECG) monitoring. Deedwania et al found a higher incidence of death among those with ischemia during daily life than those without (patients were on medication). 1 Similarly, in another study, Tzivoni et al found that the 77% of study participants that showed ischemia on ECG monitoring had worse outcomes (including revascularization) than those without ischemia.2 More recently, Gehi et al reported a twofold increase in MI and death in patients with silent ischemia during a 3.9-year follow-up of 937 patients (P<0.005).3 Thus, ischemia, with or without angina, predicts death and nonfatal MI.

As ischemia is predictive of events, its reduction or elimination reduces risk. Coronary artery bypass surgery (CABG) is indicated on this basis. This has been known about since CASS, which revealed a benefit in patients with left main coronary disease and multivascular disease who underwent CABG, making CABG the gold standard for treatment of ischemia since then. Drugs such as antiplatelets and statins reduce death, but 30 years ago this was not known. However, ACIP (Asymptomatic Cardiac Ischemia Pilot)4 tested the hypothesis that if you treat ischemia you will modify outcomes, whether in the presence of angina symptoms or not. CAD patients with ischemia on ECG monitoring were selected in order to measure the ischemic burden before randomization and after 12 weeks. Patients were randomized to 3 intention-to-treat arms, guided by: (i) angina, (ii) ischemia (ECG monitoring and ECG exercise testing), and (iii) patients sent for CABG. Although not a randomized drug trial, the idea was to compare strategies. The best ischemic control was achieved with CABG (55%), followed by ischemia-guided (45%) and angina-guided (39%) treatment. Medical treatment was a β-blocker plus nifedipine or diltiazem plus oral nitrates. The authors concluded that revascularization made the patients less prone to need a new procedure, and that no difference was observed in mortality and acute MI. However, in a recently published study by Aldweib et al in asymptomatic patients with silent ischemia who received revascularization 5 years earlier, of 769 patients (followed up for 5.7 years), 654 continued medical treatment and a new revascularization procedure was performed in 115.5 The authors concluded that a new revascularization should not be performed in patients with silent ischemia because no benefit was demonstrated.

A sub-study of BEAUTIFUL, (mortality-mortality EVAluaTion of the ß inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction)6 confirmed heart rate as a new marker/risk factor for death and MI in patients with CAD and left ventricular dysfunction (ejection fraction <40%), with less events in those with a heart rate of <70 beats per minute, establishing this as a new target.

As cardiologists, we believe that we must treat silent ischemia when it is sufficiently extensive that we can expect new events, as shown in the sub-study of COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation).7 In addition, we await new therapeutics that can support our goal of attenuating ischemia, thus promoting reduction in death and MI. I hope that the 2 randomized trials SIGNIFY (Study assessing ß the morbidity–mortality beneﬁts of the ß inhibitor ivabradine in patients with coronary artery disease) and ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) will bring us good news in this respect. Our patients will thank us greatly.

References

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Coronary artery disease (CAD) has a wide spectrum of manifestations. Angina only occurs at the end of the ischemic cascade. Myocardial metabolic perfusion, wall motion, and electrocardiographic abnormalities are all indicators of ischemia in a patient before they become symptomatic.

Certain patient groups, such as the elderly, type 2 diabetics, and women do not experience angina, or else it only manifests with atypical symptoms. Silent ischemia is estimated to occur in one-third of angina patients and an even higher proportion of diabetics. Hence, an estimation of the total burden of ischemia (frequency, severity, and duration) will be underestimated if based solely on the presence of angina.

Myocardial ischemic episodes are prognostically important even if silent. 1 In the study ACIP (Asymptomatic Cardiac Ischemia Pilot), ischemia confirmed by stress testing or ambulatory electrocardiogram predicted adverse cardiac outcomes. In another study of 2682 asymptomatic men without known CAD, exercise-induced ischemia increased mortality and the risk of acute coronary syndromes, especially when ischemia occurred at low workload. 3

These observations support the use of anti-ischemic pharmacotherapy in addition to treatments that can modify prognosis (eg, antiplatelets, statins, angiotensin-converting enzyme inhibitors) to reduce the ischemic burden even when angina is absent. Revascularization should be attempted when feasible.

Nitrates, β-blockers, calcium channel blockers, and ivabradine effectively reduce episodes of silent ischemia. Other antiischemic agents include trimetazidine and ranolazine. In ASIST (Atenolol Silent Ischemia STudy), atenolol reduced the ischemic burden in a dose-dependent fashion. This translated into a reduction in the primary end point of death, resuscitated ventricular arrhythmia, and cardiac events.

BEAUTIFUL (morBidity-mortality EvAllUaTion of the I inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction) (n=10 917) investigated ivabradine therapy in patients with CAD and left ventricular dysfunction (ejection fraction of <40%). 5 The majority (86.2%) of patients did not have limiting angina. In patients with a baseline heart rate of >70 beats per minute, ivabradine significantly reduced myocardial infarction events and revascularization. Not surprisingly, the subgroup with angina; ie, those with a larger ischemic burden, benefited more from therapy.

SWISSI I (SWiss Interventional pilot Study on Silent Ischemia type I) evaluated asymptomatic individuals without known CAD (n=54) who had silent ischemia on stress imaging. 6 Participants either received antianginal therapy or had their risk factors controlled. Those treated medically experienced fewer instances of cardiac death, nonfatal myocardial infarction, or acute coronary syndromes.

The prognostic implications of silent ischemia are irrefutable. The role of anti-ischemic therapy in the absence of angina remains controversial. It is unlikely that large randomized trials will be conducted to address this issue. Circumstantial evidence suggests that such therapy may be considered if there is documented ischemia, especially when this is determined to be extensive upon functional testing or when defined by coronary anatomy, or if there is associated left ventricular dysfunction. A specific heart rate–lowering agent may be appropriate when heart rate is elevated.

References
A symptomatic ischemic episodes among patients with known coronary artery disease (CAD) are frequent, and up to 75% of ischemic episodes (ST-segment depression ≥1 mm for ≥1 minute) may occur without pain. As mentioned in the current guidelines on stable angina, there is no doubt that prognostic treatment should be implemented in all patients with known stable ischemic heart disease (ie, angiotensin-converting enzyme inhibitors, aspirin, statins, β-blockers if recent myocardial infarction). However, anti-ischemic therapy is a more controversial issue.

Assessment of ischemia is mandatory for stratification of anti-ischemic therapy in asymptomatic CAD patients, as CAD prognosis is linked to the volume of underlying myocardial ischemia. There is no data to support establishment of any therapy if ischemia is not induced. If ischemia is present, the ischemic threshold, extension, and intensity should be assessed in order to prescribe the adequate treatment. If the ischemic threshold is high, treatment to reduce heart rate would be appropriate. If the ischemic threshold is low (ie, heart rates frequently achievable during normal life) or the severity of ischemia is relevant (ie, more than 10% of myocardial volume), we should treat the patient and a coronary angiogram should be considered. However, it must also be kept in mind that coronary revascularization in asymptomatic patients has no prognostic impact unless significant ischemia is shown on imaging stress tests despite optimal medical treatment.

The main remaining question is thus which treatment should be used. Current American guidelines make no mention of any medical therapy in asymptomatic patients. If we assume that treatment should be the same as is given to symptomatic patients, current European guidelines recommend β-blockers, calcium channel antagonists, and nitrates. If ischemia remains despite dose titration and drug combinations, then ivabradine, nicorandil, or trimetazidine should be added. However, recent data published by the REACH (REduction of Atherothrombosis for Continued Health) study group suggest that β-blocker treatment in patients with CAD with no prior myocardial infarction might not be a consistent choice in terms of prognosis. On the other hand, there is weak evidence for calcium channel antagonists and nitrates. New treatments such as ivabradine and ranolazine have more solid evidence than most of the aforementioned classic treatments, although they have always been tested on top of classic treatments. The new European guidelines on stable angina have opened up the first line of treatment to these drugs if contraindications or intolerance is present with β-blockers or non-dihydropiridinic calcium channel blockers; otherwise, they remain as add-on treatment in cases where drugs in the first step of treatment are not sufficient after adequate dose titration. In this sense, it has kept in mind that heart rate is not correctly controlled in approximately 40% of patients treated with β-blockers.

References
Coronary artery disease (CAD) is a common disorder. In the Russian Federation, over 7.5 million patients have an established diagnosis of CAD. In stable CAD, the risk of developing complications such as myocardial infarction (MI) and chronic heart failure (CHF) is 3%-4%, and cardiovascular mortality is 2%-3% per year. The main treatment goals for CAD are prevention of complications such as MI and CHF, reduction in the risk of death, and relief—partially or completely—of ischemic symptoms.

Prevention of CAD complications is achieved with antiplatelets (aspirin or clopidogrel), statins, renin-angiotensin system blockers (there is evidence for the efficacy of the angiotensin-converting enzyme inhibitors ramipril and perindopril), and β-blockers (in post-MI patients). Blood pressure control to below 140/90 mm Hg (the new target recommended in the 2013 European Society of Hypertension/European Society of Cardiology guidelines) is also very important. Emphasis should be given to heart rate (HR) control, and as shown in BEAUTIFUL (morBidity-mortality EvAlUaTion of the I f inhibitor ivabradine in patients with coronary disease and left ventricULar dysfunction), the risk of complications increases with HR above 70 beats per minute regardless of β-blocker therapy.

Treatment aimed at eliminating symptoms of angina and/or silent myocardial ischemia includes β-blockers, calcium channel blockers (CCBs), long-acting nitrates, the selective sinus node I channel inhibitor ivabradine, cytoprotective agents (trimetazidine), the late sodium channel current inhibitor ranolazine, and the potassium channel activator nicorandil. All of these drugs exert antianginal (anti-ischemic) effects proven in controlled clinical studies.

Among the aforementioned agents, evidence for prognostic improvement has only been obtained for β-blockers and exceptionally in post-MI patients. β-Blockers are recommend-
Within the population of patients with coronary artery disease (CAD), comorbidities such as impaired left ventricular (LV) function, myocardial infarction (MI), diabetes, or chronic kidney or pulmonary disease identify individuals with increased risk. Similarly, documented myocardial ischemia is a marker of poor prognosis in patients with asymptomatic CAD, who need strategies to reduce risk.

The ideal therapeutic strategy for stable CAD patients addresses both of the 2 main goals of CAD therapy: reduction in symptoms and improvement in prognosis. Effective prognostic treatment such as low-density lipoprotein lowering with statins and inhibition of thrombocyte activation reduces the risk of MI and death and is therefore recommended. However, symptomatic treatments without prognostic effects are not indicated for patients without angina. In the absence of angina or a documented prognostic action, negative effects relating to potential side effects, drug interactions, and reduced medication adherence must be avoided. Therefore, available antianginal drug therapies must be discussed with regard to their prognostic properties as well as their amelioration of symptoms.

The prognostic importance of β-blockers for CAD patients has recently become a matter of debate. The 2012 American Heart Association guidelines on stable CAD recommend β-blockers for the first 3 years after acute coronary syndromes and for all patients with impaired LV function. However, for patients with stable asymptomatic CAD without MI or who are more than 3 years post MI, the prognostic evidence in favor of β-blockers is unclear (recommendation class IIB, level of evidence C).

Nitrates are potent drugs for treatment and prevention of angina. However, a prognostic benefit has never been documented: Therefore, use of nitrates should be continuously reviewed during the course of CAD and stopped in asymptomatic patients due to lack of benefit.

Ranolazine, an inhibitor of the late sodium current, effectively reduces angina without effects on blood pressure or heart rate (HR). A prognostic effect has not been reported. Experimental and subgroup analyses of clinical studies have triggered an interesting discussion about possible antiarhythmic effects of ranolazine in atrial fibrillation, caused by mechanisms involving normalization of intracellular Na⁺ and Ca²⁺ overload, reduction in delayed afterdepolarizations, and increase in the action potential duration and effective refractory period. Ongoing studies will help understand the clinical importance of these animal data (RAFFAELLO [Ranolazin in AF Following An E L ectrical cardioversion], HARMONY [A Study to Evaluate the Effect of Ranolazine and Dronedarone When Given Alone and in Combination in Patients With Paroxysmal Atrial Fibrillation]).

The ß-channel blocker ivabradine, alone or in combination with a β-blocker, potently improves symptoms and quality of life in patients with stable angina (ADDITIONS [prActical Daily ef ficacy anD safety of Procoralan In combinaTION with ß-blockerS]). Mechanistic preclinical studies show that HR reduction with ivabradine exerts potent antithrombotic vascular effects via inhibition of vascular inflammation and oxidative stress, leading to improved endothelial function, inhibition of atherosclerotic plaque formation, improvement in arteriogenesis during ischemia, and reduction in the size of ischemic strokes. Large randomized clinical trials have documented the prognostic effects of ivabradine in patients with heart failure and CAD patients with impaired LV function. International clinical studies are under way to directly address the prognostic effects of HR reduction in CAD (SIGNIFY [Study assessInG the inTegrAted benefIt of ß-channel blocker ivabradine In patients with stable coronary artery disease], CLARIFY [prospective observational LongitudinAl Registry of patients with stable coronary artery disease]).

In summary, current strategies to improve prognosis in asymptomatic CAD patients are limited. Ongoing studies will help to identify whether HR reduction with ivabradine improves cardiovascular outcomes in patients with stable CAD, in addition to its well-documented prevention of angina and prognostic benefits for patients with heart failure.

References


Should stable CAD patients without angina receive anti-ischemic therapy?
The first task of a physician confronted with a patient—who probably consulted because of symptoms—is to soothe and find the most efficient therapy to relieve those symptoms. The second task is to treat the underlying cause and act on the asymptomatic mechanisms that will either precipitate a more severe health status or shorten life expectancy. Finally, of course, there is the primum non nocere (above all, do no harm) rule. Coronary artery disease (CAD) is a perfect example of this paradigm. The most recent guidelines for CAD patients with stable angina emphasize the goals of therapeutic management: (i) to improve prognosis by preventing myocardial infarction (MI), heart failure, and death; and (ii) to minimize or abolish symptoms. What should the physician do when these symptoms are absent? There is solid evidence backing the use of aspirin, statins, and angiotensin-converting enzyme inhibitors together with lifestyle changes (smoking cessation, regular physical activity, healthy diet, diabetes and hypertension control) to improve prognosis in CAD patients. These treatments will also be effective for silent ischemia.

Use of anti-ischemic drugs in asymptomatic CAD patients appears more controversial, at least to the “lay cardiologist.” Commonly used anti-ischemic drugs include β-blockers, siren node inhibitors, calcium antagonists, organic nitrates, and potassium channel openers. These will either directly increase coronary blood flow or reduce myocardial oxygen consumption.

Nitrates or potassium channel openers are useless in the absence of angina. These treatments are prescribed to “soothe” symptoms. The only trial showing a significant clinical benefit in this situation, IONA (Impact Of Nicorandil in Angina), involved patients with stable angina. Use of heart rate (HR)-lowering agents for this indication is more difficult. There is clear evidence showing poor prognosis for major cardiovascular events with increasing HR. There is also solid evidence showing the benefits of β-blockers in the immediate post-MI period and in patients with altered ejection fraction. However, if use of β-blockers is a cornerstone in stable CAD patients, the recent study by Bangalore et al from the REACH (REduction of Atherothrombosis for Continued Health) registry might have shaken its foundations. In this study of 21,860 stable outpatients with or without CAD followed over approximately 4 years, use of β-blockers was not associated with lower risk of composite adverse cardiovascular events. This study showed a significant 18% increase in adverse cardiovascular events with β-blockers in patients without evidence of CAD, but with CAD risk factors. This is in agreement with a previous report showing that in contrast with patients with MI and heart failure, in hypertensives, β-blockers increased the risk of cardiovascular events and death.

Similarly, in BEAUTIFUL (morBidity-mortality Evaluation of the I, inhibitor ivAbradine in patients with coronary disease and left ventricular dysfunction), HR lowering with ivabradine in patients with CAD and altered left ventricular ejection fraction did not show any significant overall clinical benefit. However, cardiovascular events were significantly related to resting HR levels. This suggests that fixing a target HR might be of prognostic interest for CAD patients.

Use of efficient HR-reducing pharmacological agents without any effect on hemodynamic or myocardial contractility in CAD patients might be beneficial. There is no data supporting this, but part of the answer will be provided by the ongoing SIGNIFY study (Study assessing the morbidity–mortality benefits of the I, inhibitor ivabradine in patients with coronary artery disease) assessing the effect of HR reduction with ivabradine in a large cohort of patients with resting HR ≥70 beats per minute and stable CAD without systolic dysfunction.

In conclusion, there is little evidence backing the use of anti-ischemic therapy in asymptomatic CAD patients with preserved ejection fraction. Future trials in large cohorts of stable and asymptomatic patients will hopefully help us answer this question in the near future.

References
Ischemia is deemed silent when objective coronary insufficiency, as documented in a stress test, is unaccompanied by angina or angina equivalents. In 1981, Cohn classified myocardial ischemia into 3 groups: type I, asymptomatic individuals without known coronary artery disease; type II, patients with prior myocardial infarction and silent ischemic episodes; and type III, patients with known coronary artery disease and both symptomatic and asymptomatic ischemic episodes.

Silent myocardial ischemia is common. Estimates of its prevalence, despite the obvious methodological difficulties involved, range from 2%-4% among apparently healthy individuals. Cohn type III silent ischemia is the most frequent. Up to 50% of patients with symptomatic stable angina also experience silent ischemic episodes. In such individuals, three-quarters of all ischemic episodes can be silent. In other words, overt angina is only the tip of the iceberg.

Silent angina has been underinvestigated, with most trials focusing on symptomatic patients. However, myocardial ischemia has exactly the same outcome in asymptomatic patients as in their symptomatic counterparts. It may even be more dangerous: symptomatic patients at least have angina as an ischemia “alarm bell,” whereas asymptomatic patients are unaware of the myocardial ischemia threatening their daily lives.

In 1987, Gottlieb et al determined the prognostic implication of silent myocardial ischemia in a group of 70 patients discharged with a diagnosis of unstable angina and followed for 2 years. Ambulatory electrocardiogram (ECG) showed silent myocardial ischemic episodes in just over half of these patients (n=37), who also had a higher risk of death or myocardial infarction than patients without silent ischemic episodes, despite receiving similar anti-ischemic treatment.

SWISSI-I (SWiss Interventional Study on Silent Ischemia type I) was a pilot open-label study in patients with at least 1 cardiovascular risk factor and Cohn type I silent ischemia, ie, individuals with stress test evidence of myocardial ischemia, no angina symptoms, and no known coronary artery disease. Fifty patients were randomized to risk factor control or medical treatment (aspirin, plus antianginal drugs: β-blockers, dihydropyridine calcium channel blockers, or both) and were followed for 10 years. A primary end point (cardiac death, myocardial infarction, acute coronary syndrome requiring hospitalization or revascularization) occurred in 12% of the medical treatment group compared with 61% of the risk factor control group. Medical treatment was also more effective in preventing exercise-induced myocardial ischemia and preserving left ventricular function. Interestingly, no patient died over the 10 years in the medical treatment group, while total mortality in the risk factor control group was 1.1% per year, driven mostly by cardiac death.

In summary, silent myocardial ischemia is a common condition that often goes undiagnosed. Few data on prevalence and optimal therapy are available, as few trials have included asymptomatic patients. However, the best practice is to treat silent ischemia with anti-ischemic therapy to prevent accidents and ultimately improve prognosis. Interestingly, episodes of silent myocardial ischemia can also occur in patients with symptomatic coronary artery disease. In such cases, they have negative prognostic significance.

References
Silent myocardial ischemia (SMI) may occur in about half of asymptomatic patients with stable coronary artery disease (CAD). It is diagnosed in patients without symptoms on stress testing, but with transient ST-segment deviation, wall motion abnormalities, or a perfusion defect characteristic of ischemia. In some studies, it is assessed on ambulatory 24- to 48-hour electrocardiogram monitoring. SMI, either in daily life or provoked by exertion, is associated with cardiovascular death and myocardial infarction (MI). CAD patients with silent ischemia have similar or worse prognosis than symptomatic patients.

Possible mechanisms underlying myocardial ischemia relate to increased oxygen demand (eg, increased heart rate) and insufficient supply (eg, diminished flow due to narrowed lumens, vasoconstriction, microvascular perfusion abnormalities secondary to endothelial dysfunction). Existing and evolving therapies impact 1 or more of these mechanisms. Data from studies comparing medical and surgical regimens in patients with SMI remain controversial. In ACIP (Asymptomatic Cardiac Ischemia Pilot), revascularization was superior to both angina-guided and ischemia-guided medical therapy for SMI suppression and improvement in 1-year outcomes. Bypass surgery was beneficial in reducing asymptomatic exertion ischemia compared with coronary angioplasty. Of note, this study was performed in the 1990s when treatment modalities differed from today, which may explain the superiority of revascularization. The more recent study COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive drug Evaluation) showed that the efficacy of optimal medical therapy (OMT) alone was not inferior to that of OMT in combination with percutaneous coronary intervention (PCI) in stable CAD patients. Another recent study, in SMI patients, suggested repeat revascularization provided no survival benefit versus medical therapy alone.

SMI detection and prognostic implications may be partially dependent on the manner of ischemia evaluation. Newer imaging techniques are more precise and informative for ischemia detection and evaluation. A recent myocardial perfusion single-photon emission computed tomography imaging study involving patients with documented CAD demonstrated that SMI worsening is an independent predictor of death and MI. Ischemia reduction may therefore be a therapeutic target and could be objectively assessed to measure treatment efficacy. More CAD patients on medical therapy alone developed ischemia worsening than with PCI and coronary artery bypass grafting. Most patients received aspirin, lipid-lowering agents, and β-blockers. While use of calcium channel blockers (CCBs) or β-blockers to reduce ischemia improves survival and decreases ischemic event rates, little is known about the impact of other anti-ischemic drugs and metabolic therapy on the disease course in CAD patients with SMI. Dual antiplatelet therapy, anti-ischemic agents such as ivabradine or ranolazine, and trimebutine may have beneficial effects on ischemia and improve clinical outcomes. Although no persuasive data exists on the survival benefits of these drugs in asymptomatic ischemia, current data support their use to reduce ischemia. Tardif et al demonstrated that addition of ivabradine to β-blocker improves exercise capacity in stable angina patients compared with β-blocker alone. Stone et al investigated the effects of ranolazine, with data suggesting that it reduces ST-segment depression and improves rate-pressure product during exercise, possibly due to improvement in regional coronary blood flow, inhibiting myocardial late sodium inward currents associated with ischemia.

Summarizing the available data on medical treatment of SMI patients and the efficacy of revascularization, it may be advisable to use OMT in all patients with asymptomatic ischemia and to advise revascularization if indicated. OMT should include antiplatelet therapy, lipid-lowering drugs, and anti-ischemic drugs such as β-blockers and/or CCBs. Administration of anti-ischemic agents other than β-blockers to patients with silent ischemia needs further investigation in large-scale trials, and may possibly be reserved for patients with angina symptoms.

References
The natural history of angiographically-confirmed coronary artery disease (CAD) is unpredictable, alternating between periods of stability and instability, as coronary atherosclerosis is a generalized and progressive disease with uncertain individual variations.

In recent years, the first clinical presentation of CAD has often been an acute coronary syndrome (ACS) resulting in early myocardial revascularization and treatment of culprit lesions. However, coronary interventions may not alter the natural history of CAD, and nonculprit, nonobstructive, or undetected lesions can progress, potentially causing future adverse events.

Anginal pain is usually considered the warning signal for the presence of myocardial ischemia. Established recommendations exist for risk assessment and treatment of confirmed/suspected angina, and have the purpose of controlling symptoms, before or after revascularization, and improving prognosis. However, angina is difficult to exclude clinically in some patients due to symptomatic equivalents (dyspnea, fatigue, or diaphoresis on exertion) or comorbidities.

Studies have consistently suggested that prognosis in stable CAD is particularly driven by objective ischemia. It is also known that most ischemic episodes are asymptomatic. The absence of angina may enable a patient to continue a normal and sometimes stressful life, including performance of exercise, potentially causing ischemia-induced arrhythmias or ACS. This is particularly pertinent in diabetic patients in whom autonomic nerve dysfunction may cause a lack of perception of ischemic symptoms. Recent studies with long-term follow-up after percutaneous coronary intervention also confirm the importance of disease progression and silent ischemia for future events. In the absence of proper diagnostic tests to detect vulnerable plaques on an individual basis, it makes sense that, today, a major clinical challenge is prevention of plaque instability and asymptomatic ischemia and avoidance of ACS and unexpected sudden death. Therefore, asymptomatic patients, particularly those with documented ischemia, should be managed similarly to patients with angina.

Along with patient education and lifestyle interventions (smoking cessation, diet, weight loss, regular physical exercise), guidelines have established adequate medical therapy for risk factor modification and prevention of myocardial infarction and death. Optimal medical therapy includes statins, antplatelets, angiotensin-converting enzyme inhibitors, and β-blockers. The long-term prognostic value of β-blockers, both after an infarction with good left ventricular function and in patients without angina, has recently been questioned.

Reduction in silent ischemic episodes has also been documented with optimal medical therapy. However, studies from the late 1990s (ACIP [Asymptomatic Cardiac Ischemia Pilot], TIBET [Total Ischaemic Burden European Trial]) showed that the precise anti-ischemic regimen may be less important as long as the mean heart rate (HR) is sufficiently reduced. High HR is the most important trigger for myocardial ischemia, causing an imbalance between myocardial oxygen supply and demand, as well as endothelial dysfunction, plaque rupture, and progression of atherosclerosis.

HR has been established as a risk marker for morbidity and mortality in various populations (healthy, hypertensive, CAD, etc). Studies with ivabradine, a pure HR-reducing agent, have shown that HR is also a risk factor in patients with heart failure, depressed ventricular function, and CAD. Ivabradine has the advantage over β-blockers of providing coronary vasodilation without negative inotropic effects or blood pressure changes, along with beneficial effects on endothelial function. The anti-ischemic effects of ivabradine have been confirmed in many studies when given in addition, or as an alternative to, β-blockers. Results of SIGNIFY (Study assessInG the morbidity–mortality beNefits of the I f inhibitor ivabradine in patients with coronarY artery disease) may establish the long-term prognostic value of ivabradine in patients without left ventricular dysfunction.

In conclusion, anti-ischemic therapy should be given to all CAD patients, even in the absence of angina. HR should be used for risk stratification and to guide optimal medical therapy.
Coronary artery disease (CAD) is characterized by atherosclerotic luminal narrowing of coronary vessels, which causes restricted blood flow to the myocardium and symptoms of angina. In stable CAD, coronary luminal narrowing is fixed and shows no recent progression, and it is usually characterized by an absence of symptomatology.

Anti-ischemic agents are paramount in CAD treatment, and include a broad spectrum of medications: nitrates, calcium channel blockers (CCBs), β-blockers, and other novel agents. Nitrates are well established for angina treatment, with more than 70 years of clinical use. By directly causing endothelial relaxation via nitrous oxide, nitrates vasodilate coronary arteries and redistribute blood flow to ischemic myocardial tissue, increasing oxygen supply and rapidly resolving ischemic insults. Indeed, even with administration of small doses of sublingual nitrates, one can observe dramatic differences in coronary vessel sizes during angiography. While efficacious in abating symptoms of angina and CAD, randomized trials with nitrates have not shown a survival benefit for CAD patients.

Similarly, CCBs are well established in the treatment of angina. Coronary blood flow is increased, with smooth muscle relaxation and vasodilation of coronary arteries. While useful in treating angina through relief of ischemia, insufficient data exist to show any consistent reduction in mortality. Furthermore, short-acting CCBs are associated with increased cardiac events and myocardial infarction.

While coronary blood flow may be sufficient to meet myocardial oxygen requirements at rest, obstruction prevents blood flow from increasing during exertion or periods of increased oxygen demand, causing angina in CAD. β-Blockers are used as first-line treatment, attenuating catecholamine action and thereby reducing contractility, myocardial oxygen demand, afterload, and heart rate (HR). β-Blockers have been shown to reduce the frequency and severity of acute angina attacks, with evidence that they also reduce mortality, especially post myocardial infarction. Patients on β-blockers partaking in physical activity will notice significant blunting of HR response to exercise, thus reducing myocardial oxygen demand and potentially increasing exercise tolerance.

Ivabradine is a novel anti-ischemic agent that acts by specifically inhibiting the I<sub>f</sub> current in the sinoatrial node. This results in a lower HR at rest and during exercise. Ivabradine has no negative inotropic effects and can therefore lower a patient’s HR exclusively without affecting blood pressure. Clinical trials have shown that ivabradine increases exercise tolerance and significantly reduces the number of angina attacks. Although there is evidence showing that ivabradine improves survival in heart failure patients, few trials have shown improved cardiac outcomes in stable CAD patients.

Many randomized clinical trials have correlated increased exercise capacity with better clinical outcomes in CAD patients. Patients who underwent cardiac rehabilitation after hospitalization showed a significant 25% decrease in mortality, compared with those not undergoing rehabilitation. Improving exercise tolerance has a dramatic effect on survival. We quantify a patient’s exercise capacity using metabolic equivalents of task (METs), whereby 1 MET represents a patient’s metabolic rate at rest. Each extra MET of activity achieved during exercise confers a 13% reduction in mortality. Patients who have high activity levels and can perform up to 13 METs of activity have a 60% reduction in mortality compared with sedentary individuals. Therefore, it can be argued that medications that increase exercise tolerance potentially confer a survival benefit. β-Blockers and ivabradine lower maximal HR during exercise, thereby increasing exercise capacity and effort tolerance, potentially improving patient survival.

Overall, there may still be a role for anti-ischemic agents in stable CAD, particularly those that increase exercise capacity.
Silent (asymptomatic) myocardial ischemia is the most common manifestation of coronary heart disease (CHD), accounting for more than 75% of ischemic episodes during daily life. The prognostic importance and optimal management of silent myocardial ischemia has been the subject of considerable debate, and the evidence base to guide management has been considerably smaller than that for symptomatic ischemia. Several studies indicate that silent ischemia is associated with higher morbidity and mortality in patients with CHD. Moreover, in such patients, the total amount of ischemic myocardium may be the most important predictor of prognosis.

Asymptomatic coronary ischemia is usually identified during stress testing, the indication for which is often a preoperative evaluation or a screening program. Once ischemia is detected, even in subjects without symptoms of angina, the ischemic burden is generally quantified and the coronary anatomy defined to more precisely stratify the risk in the patient.

Occasionally, this process may identify high-risk coronary anatomy that warrants revascularization. More often, however, the coronary anatomy is not high risk, and the patient is deemed suitable for medical management. It is particularly important to recognize that even in asymptomatic subjects, the studies COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) and BARI 2D (Bypass Angioplasty Revascularization Investigation in type 2 Diabetes) demonstrated that an initial management strategy of revascularization and optimal medical therapy (OMT) does not reduce the risk of death or myocardial infarction in stable ischemic heart disease patients compared with OMT alone. Also, asymptomatic patients with previous revascularization and inducible ischemia on myocardial perfusion imaging realize no survival benefit from repeat revascularization. In this group of post-revascularization patients, an ischemia-based treatment strategy did not alter mortality. Asymptomatic patients with atherosclerotic coronary artery disease and ischemia should be managed with OMT. In contrast with patients who have angina, there is no robust evidence base for instituting antianginal therapy in asymptomatic patients. The risk factor profile of each individual patient should be studied, and a careful search should be made for underlying diabetes mellitus, as diabetics have an increased incidence of silent ischemia. In the majority of patients, the presence of atherosclerotic coronary artery disease indicates that a secondary prevention strategy should probably be followed, even though, strictly speaking, they have not had a vascular event. The patient should be counseled on the issue of silent ischemia, and the diet and lifestyle of the patient shall be discussed and optimized. Exercise should not be withheld, and an attempt to attain ideal body weight should be instituted.

A lipoprotein profile should be arranged and the patient started on statin therapy with a target level for low-density lipoprotein cholesterol of 1.8 mmol/L. Tight blood pressure control should be achieved in all patients, and if they have a history of hypertension, an echocardiogram should be obtained and left ventricular mass documented. Subjects with hypertensive heart disease may have silent ischemia even in the absence of flow-limiting coronary stenoses. The initial agent of choice in hypertensive subjects with atherosclerotic coronary disease should be an angiotensin-converting enzyme inhibitor, given their antithrombotic properties demonstrated in the study HOPE (Heart Outcomes Prevention Evaluation). Antiplatelet therapy is generally used in most patients.

Although β-blockers, nitrates, and other antianginal drugs are commonly used in patients with angina, there is no large body of evidence to support use of these agents in subjects without angina. Further clinical trials are needed to address the important question of optimal heart rate and hemodynamic goals in asymptomatic ischemia. Until such evidence exists, it is appropriate to manage the atherosclerotic process with OMT.

References
Silent myocardial ischemia (SMI) is considered the most frequent manifestation of coronary artery disease (CAD). SMI is an important public health issue; its presence confers a higher risk of adverse clinical outcomes, coronary events, and cardiac death. Studies have shown that SMI detected in the general population (without known CAD) predicts a fivefold increased risk of coronary events and cardiac death during a 10-year period. Episodes of myocardial ischemia without chest pain or other anginal equivalents have been shown to occur in 25%-50% of patients with CAD. The prevalence of SMI in patients with angina, renal disease, diabetes, or previous myocardial infarction is significantly higher.1,2

Although early detection and treatment of SMI may prevent many coronary events and episodes of sudden cardiac death, the benefits of SMI treatment remain controversial and questionable. For example, Ferreira et al showed that during daily activities, SMI is present and frequent, even in patients receiving medication. Paradoxically, it occurs at a lower heart rate (HR) than that observed during exercise testing and is preceded by slight variations in HR. Alterations in systolic blood pressure and HR occur before and after episodes of myocardial ischemia, thus confirming that the factors that determine oxygen consumption interfere with the genesis of myocardial ischemia even in patients receiving antianginal medication.3

The main therapeutic approach to myocardial ischemia should be based on antianginal, lipid-lowering, antihypertensive, and metabolic drugs. If anti-ischemic combination therapy with multiple medications is not effective, revascularization therapy should be considered. It is worth noting that the addition of percutaneous coronary intervention to optimal medical therapy did not decrease nonfatal cardiac events in patients with SMI, but has shown a trend toward fewer deaths.4 Progress in the early detection and treatment of CAD has allowed us to reconsider screening for SMI in the hope of achieving an early CAD diagnosis that will lead to more effective pathophysiological therapy and decreased cardiovascular complications and mortality rates. Nevertheless, the benefits of systematic SMI screening remain controversial, because screening for SMI in the general and low-risk population (either on ambulatory monitoring or exercise testing) is unfeasible and inefficient due to its poor sensitivity and specificity.5 By contrast, diabetic retinopathy in asymptomatic type 2 diabetic patients, for example, is considered to be a high-risk condition for SMI development, and thus affected patients become a target for CAD screening.6 The results of a meta-analysis of the studies DYNAMIT (Do You Need to Assess Myocardial Ischemia in Type 2 diabetes) and DIAD (Detection of Ischemia in Asymptomatic Diabetics) suggest that the systematic detection of silent ischemia in high-risk asymptomatic patients is unlikely to provide any major benefit on hard outcomes in patients whose cardiovascular risk is controlled by optimal medical treatment.6 Awareness of the incidence of SMI in high-risk populations can reduce cardiovascular morbidity and mortality rates.

In conclusion, on the basis of our current knowledge and evidence, CAD patients with SMI should undoubtedly be treated with anti-ischemic medications, and therapeutic efficacy should be guided by ischemia, whether symptomatic or silent. Further evaluation of techniques for detection and management of SMI in well-designed, prospective, randomized controlled multicenter trials in various patient populations is also necessary.

References
Clinical benefits of Procoralan (ivabradine): evidence and perspectives

by I. Elyubaeva, France

Procoralan (ivabradine) is the first selective and specific If inhibitor, and provides pure heart rate (HR) reduction without altering myocardial contractility, the cardiac conduction system, or coronary vascular resistance. Experimental data have demonstrated the specific nature of the HR-lowering action of ivabradine and suggest that the selective mechanism by which HR slowing is achieved allows the maximum realization of benefits from HR reduction for improved coronary perfusion and pump efficiency. The ability of ivabradine to affect angina symptoms and myocardial ischemia and to prevent coronary events makes it an important agent in the management of patients with coronary artery disease (CAD). With its pharmacological and clinical properties, ivabradine is a disease-modifying treatment for patients with chronic heart failure (CHF). The results of SHIFT (Systolic Heart failure treatment with the If inhibitor ivabradine Trial) show that ivabradine is particularly suited to fulfill unmet needs in the treatment of CHF patients, improving symptoms and well-being along with outcomes. This evidence supports ivabradine’s importance as an essential therapeutic modality to enhance management of patients with CAD or CHF. The ongoing SIGNIFY trial (Study assessInG the morbidity-mortality benefits of the If inhibitor ivabradine in patients with coronary artery disease) seeks to advance a new treatment paradigm by testing the hypothesis that HR reduction improves long-term clinical outcome in stable CAD patients without clinical HF. The results should provide insight into a role for ivabradine in the management of patients with stable CAD.

Medicographia. 2014;36:89-97 (see French abstract on page 97)

Pure heart rate reduction with ivabradine: anti-ischemic effect and cardiovascular protection

Procoralan (ivabradine) is a specific heart rate (HR)-lowering agent, which has selective action on pacemaker activity in the sinoatrial node of the heart, resulting in important differences compared with nonselective HR-reducing agents, such as β-blockers.¹ By inhibiting If—an ionic current that modulates pacemaking activity—in the sinus node, ivabradine lowers HR without directly affecting myocardial contractility (or relaxation), ventricular repolarization, or intracardiac conduction.²

Physiological changes in HR affect mainly the duration of diastole, with lower HR leading to prolongation of diastolic time, both in absolute terms and as a fraction of the cardiac cycle, facilitating myocardial perfusion.³ Ivabradine, similarly to physio-
logical HR reduction, lowers HR essentially by prolonging diastole. In addition, ivabradine maintains coronary vasodilation during exercise. By contrast, β-blockers, due to their negative effect on myocardial contractility, tend to prolong systole as well, reducing their beneficial effect on diastolic time as a fraction of the cardiac cycle. β-Blockers may affect vasomotion in the coronary circulation by unmasking α-adrenergic vasoconstriction, resulting in constriction of large and small coronary arteries during exercise. The experimental data suggest that pharmacological HR reduction with ivabradine resembles physiological change in HR more closely than what occurs with β-blockade, in that physiological changes in diastolic time fraction, LV relaxation, and coronary vasomotion are not compromised by other unwanted cardiac effects. In consequence, maximum benefits of HR reduction for improved coronary perfusion can be realized.

By reducing HR, ivabradine decreases myocardial oxygen consumption and increases myocardial perfusion, both of which preserve cardiac energy metabolism, which is profoundly depleted during HF. Sustained HR reduction with ivabradine was found to improve cardiac function by significantly decreasing left ventricular (LV) systolic diameter and increasing fractional shortening. Ivabradine preserved cardiac output due to increased stroke volume, reduced LV collagen density, and increased LV capillary density. These experimental data show that long-term HR reduction with ivabradine optimizes energy consumption, reverses remodeling, and prevents disease progression in HF.

Endothelial dysfunction is a common feature of all cardiac diseases, including coronary artery disease (CAD) and chronic heart failure (CHF). HR lowering with ivabradine may improve endothelial function and inhibit development and progression of atherosclerotic plaque. In dyslipidemic mice expressing human apoprotein B-100, 3 months’ treatment with ivabradine completely prevented deterioration of endothelial-dependent vasodilation in the renal and cerebral arteries. In another model, with severe hypercholesterolemia in apolipoprotein E–deficient mice, ivabradine treatment improved endothelial function, and reduced atherosclerotic plaque area in the aortic root (by >40%) and ascending aorta (by >70%). These beneficial effects on endothelial function and slowing of development of atherosclerosis may contribute to the reduction in cardiac events seen in the clinical setting.

Clinical benefits of pure HR reduction with ivabradine

The results of clinical trials are consistent with the importance of HR in pathophysiology of CAD and CHF, supporting the value of pure HR reduction in management of these patients.

Clinical benefits of HR reduction with ivabradine in stable CAD

Consistent with this advanced understanding of the importance of HR in the pathophysiology of CAD, HR 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 (CV) events.

Reduction in angina attacks and improvement in quality of life

Ivabradine substantially reduced the frequency of angina attacks and the consumption of short-acting nitrates compared with placebo. Antianginal efficacy of ivabradine was confirmed in the INITIATIVE study (INternational TrIAl on the Treatment of angina with IVabradinE versus atenolol), which included 939 patients with stable angina: the number of angina attacks was decreased at 4 months by 1.6 with ivabradine and by 1.2 with atenolol 100 mg once daily.

Selected abbreviations and acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACE</td>
<td>angiotensin-converting enzyme</td>
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<tr>
<td>ADDITIONS</td>
<td>prActical Daily efficacy anD safety of Procoralan in combinaTION with betablockerS (trial)</td>
</tr>
<tr>
<td>ASSOCIATE</td>
<td>evaluation of the Antiangial efficacy and Safety of the aSsociation Of the i, Current Inhibitor ivAbradine with a beTa-blockEr</td>
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<tr>
<td>BEAUTIFUL</td>
<td>morBidity-mortality EvAluaTion of the i, inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction</td>
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<tr>
<td>bpm</td>
<td>beats per minute</td>
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<tr>
<td>CAD</td>
<td>coronary artery disease</td>
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<tr>
<td>CARVIVA HF</td>
<td>effect of CARVedilol, IVabradine or their combination on exercise capacity in patients with Heart Failure (trial)</td>
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<tr>
<td>CHF</td>
<td>chronic heart failure</td>
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<tr>
<td>CV</td>
<td>cardiovascular</td>
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<tr>
<td>EQ-5D</td>
<td>EuroQol 5 Dimension (questionnaire)</td>
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<tr>
<td>EQ-AD</td>
<td>EuroQol Anxiety/Depression (dimension score)</td>
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<td>HF</td>
<td>heart failure</td>
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<tr>
<td>HR</td>
<td>heart rate</td>
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<tr>
<td>INITIATIVE</td>
<td>INternational TrIAl on the Treatment of angina with IVabradinE versus atenolol</td>
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<tr>
<td>KCCQ</td>
<td>Kansas City Cardiomyopathy Questionnaire</td>
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<tr>
<td>LV</td>
<td>left ventricular</td>
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<tr>
<td>LVEF</td>
<td>left ventricular ejection fraction</td>
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<tr>
<td>LVSD</td>
<td>left ventricular systolic dysfunction</td>
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<tr>
<td>MI</td>
<td>myocardial infarction</td>
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<tr>
<td>MRA</td>
<td>mineralocorticoid receptor antagonist</td>
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<tr>
<td>NYHA</td>
<td>New York Heart Association</td>
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<tr>
<td>QOL</td>
<td>quality of life</td>
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<tr>
<td>RRR</td>
<td>relative risk reduction</td>
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<tr>
<td>SHIFT</td>
<td>Systolic Heart failure treatment with I, inhibitor ivabradine Trial</td>
</tr>
<tr>
<td>SIGNIFY</td>
<td>Study assessInG the morbidity–mortality beNe-fits of the I, inhibitor ivabradine in patients with coronary artery disease</td>
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</table>
In another double-blind, parallel-group, noninferiority trial in 1195 patients with chronic stable angina and documented CAD, ivabradine 7.5 mg twice daily produced substantial antianginal efficacy similar to amlodipine 10 mg once daily, reducing the number of angina attacks by about two-thirds and the short-acting nitrates consumption by about one-half across the study.15

The efficacy of ivabradine in reducing the frequency of angina symptoms was also confirmed in a 1-year study.15 Treatment with ivabradine 5 mg and 7.5 mg twice daily showed significant reductions in angina attack frequency from 50% to 67%, approximately relative to baseline at 1 year of treatment.

Substantial antianginal efficacy of ivabradine is confirmed under conditions seen in day-to-day practice as well, in the large open-label, multicenter ADDITIONS study (prActical Daily efficacy anD safety of Procoralan In combinaTION with beta-blockingerS [trial]) conducted in a broad range of patients with stable angina.14 Ivabradine added to β-blockers in 2330 patients with stable angina resulted in significant reduction of angina attacks and short-acting nitrate consumption (from 1.7 to 0.3 and from 2.3 to 0.4 units per week, respectively).14 In line with reduction in angina attacks, ivabradine improved quality of life (QOL) assessed by the EuroQol 5 Dimension (EQ-5D) questionnaire (both the EQ-AD index [EuroQol Anxiety/Depression dimension score], as well as visual analog scale) throughout 4 months of therapy with ivabradine (Figure 1).14

◆ Anti-ischemic efficacy and improvement of exercise capacity
Ivabradine showed significant anti-ischemic efficacy compared with placebo in the randomized, double-blind study.15 The efficacy of ivabradine was confirmed compared with representative examples of β-blockers and calcium antagonists, which are widely used for angina therapy. A relevant anti-ischemic effect of ivabradine, indicated by the increase in time to 1-mm ST-segment depression by approximately 1.5 minutes, was demonstrated in the INITIATIVE study.11 At peak drug activity at 4 months, the time to 1-mm ST-segment depression was increased by 108.4 seconds with ivabradine 7.5 mg twice daily, and 140.5 seconds with atenolol 100 mg once daily. The group receiving ivabradine 7.5 mg twice daily showed an increase in total exercise duration at the trough of drug activity of 86.8 seconds compared with 78.8 seconds in the atenolol 100 mg once daily group, and noninferiority was demonstrated for all exercise tolerance test parameters (P<0.001).

The ASSOCIATE trial (evaluation of the Antianginal efficacy and Safety of the aSsociation Of the β-current Inhibitor ivA-bradine with a beTa-blockEr) examined the effects of ivabradine in patients with chronic stable angina pectoris receiving β-blocker therapy.15 This double-blind, randomized, placebo-controlled trial in 889 patients clearly demonstrates that ivabradine in patients with stable angina receiving the β-blocker atenolol provides further significant improvement in all parameters of the exercise test at 2 and 4 months. Importantly, despite the fact that combination therapy is widely used in clinical practice to achieve adequate control of angina, clinical trials evaluating combination therapy have yielded inconsistent results. This makes ivabradine with β-blockers the best evidence-based combination therapy for angina patients.

The importance of increases in HR during daily activity due to physical or emotional stress as a trigger of myocardial ischemia is well established and explains the crucial need to prevent excessive increases in HR.16 A recent analysis from the ASSOCIATE trial further reinforced the importance of HR reduction to ensure anti-ischemic efficacy and demonstrated that ivabradine significantly improves exercise capacity whatever the baseline HR, whether it was above or below the median level of 65 beats per minute (bpm) (Figure 2, page 92).16

In a study comparing the efficacy of a combination of ivabradine 7.5 mg twice daily plus bisoprolol 5 mg once daily versus the full dose of bisoprolol (10 mg once daily) in patients with stable angina and LV systolic dysfunction (LVSD), 2 months of treatment with ivabradine substantially reduced the mean weekly number of angina attacks compared with bisoprolol alone (from 3.3 to 1.7 vs from 3.2 to 2.5, respectively; P between groups is 0.041).17

◆ Improvement in coronary flow reserve
The effect of ivabradine on coronary flow velocity and coronary flow reserve was evaluated in a study in 21 patients with stable CAD. Coronary flow velocity measurements in a non-

Figure 1. Quality of life index EQ-5D at baseline and after 1 and 4 months of treatment with ivabradine.
Abbreviation: EQ-5D, EuroQol 5 Dimension (questionnaire).
culprit vessel were taken using a Doppler guidewire, at rest and after adenosine administration to achieve maximal hyperemia. There was a significant increase in coronary flow reserve after short-term treatment with ivabradine (1 week). Improvement in coronary flow reserve may have profound clinical implications, as it predicts long-term adverse CV outcomes.

**Prevention of CV events in symptomatic patients with LVSD**
An analysis in 1507 patients with symptoms of angina at baseline in the BEAUTIFUL trial (morBidity-mortality Evaluation of the If inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction) evaluated the prognostic benefit of ivabradine in this population. The reduction in the primary end point of the study (CV death, myocardial infarction [MI], or hospitalization for heart failure [HF]) was 24% in the whole group of patients with limiting angina and 31% in the group with baseline HR ≥ 70 bpm. The primary end point appears to be driven by the coronary outcomes, as there was a 42% reduction in the risk for hospitalization for fatal and nonfatal MI in patients with limiting angina treated with ivabradine (Figure 3A). The reduction in the risk of CV outcomes was even greater in patients with angina and HR ≥ 70 bpm, notably with a significant 73% ivabradine-related reduction in hospitalization for fatal and nonfatal MI (Figure 3B) and a 59% reduction in coronary revascularization. These findings suggest benefits of ivabradine beyond the control of anginal symptoms and show the potential of ivabradine to modify the clinical course of CAD. Important insight into the role of ivabradine in the management of patients with stable CAD will be provided by the ongoing SIGNIFY trial (Study assessing InG the morbidity–mortality benefits of the If inhibitor ivabradine in patients with coronary artery disease). SIGNIFY is currently evaluating the efficacy of ivabradine in patients without HF and LVSD. It includes more than 16,850 patients from 47 countries with stable CAD, an ejection fraction above 40%, and no clinical sign of HF. The results of this trial will provide new insight into the role for ivabradine in the management of patients with stable CAD.

![Figure 2](https://example.com/figure2.png)

**Figure 2.** Treatment effect (ivabradine versus placebo) on change in exercise tolerance test criteria between baseline and study’s end (4 months), according to resting HR at baseline (≤ 65 bpm or > 65 bpm). Abbreviations: bpm, beats per minute; ETT, exercise tolerance test. After reference 18: Tardif et al. Int J Cardiol. 2013;168(2): 789-794. © 2012, Elsevier Ireland Ltd.

<table>
<thead>
<tr>
<th>Total exercise duration</th>
<th>Favors placebo</th>
<th>Favors ivabradine</th>
<th>P value</th>
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<tr>
<td>&gt; 65 bpm</td>
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<td>Time to limiting angina</td>
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<td>≤ 65 bpm</td>
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<td>Time to onset of angina</td>
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<td>P=0.001</td>
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<td>≤ 65 bpm</td>
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<td>Time to 1-mm ST depression</td>
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<td>≤ 65 bpm</td>
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**Figure 3.** Kaplan-Meier time-to-event curves by treatment group for hospitalization for fatal and nonfatal myocardial infarction in patients with limiting angina at baseline (A) and in patients with limiting angina and resting heart rate ≥ 70 bpm at baseline (B). Abbreviations: bpm, beats per minute; CI, confidence interval; HR, heart rate; MI, myocardial infarction. After reference 20: Fox et al. Eur Heart J. 2009;30(19):2337-2345. © 2009, The Author.
Clinical benefits of HR reduction with ivabradine in HF

Reduction in the risk of major outcomes related to HF
The effect of ivabradine in improvement of prognosis in HF has been successfully tested in the SHIFT trial (Systolic Heart failure treatment with the If inhibitor ivabradine Trial). This randomized placebo-controlled clinical trial evaluated the effects of ivabradine, in addition to guideline-recommended therapies, on morbidity and mortality in 6558 patients with moderate to severe chronic HF and LVSD (LV ejection fraction [LVEF] <35%) and a resting HR ≥70 bpm (median follow-up was 22.9 months). After 28 days, ivabradine reduced HR by 15.4 bpm (10.9 bpm placebo-corrected). The primary composite end point (CV death or hospital admission for worsening HF) was significantly reduced by 18% (P<0.0001) (Figure 4A). Ivabradine significantly reduced both hospitalization for HF (relative risk reduction [RRR], 26%; P<0.0001) and HF death (RRR, 26%; P=0.014) (Figure 4B and C).

Reduction in the burden of hospitalizations related to worsening HF
Despite current intensive multidrug therapies, readmission rates following HF remain very high. SHIFT analysis explored the effect of ivabradine on recurrent hospitalizations for HF as well as on the total HF hospitalization burden. The results show that ivabradine substantially reduced the total number of HF hospitalizations by 25% (P=0.0002). Over 2 years of follow-up, ivabradine substantially reduced the risk of recurrent HF hospitalization: 34% reduction (P<0.001) in the risk of second hospitalization, 29% reduction (P<0.012) in the risk of third hospitalization (Figure 5). Similar results for HF hospitalization were seen in the higher risk subgroup of patients with a HR of ≥75 bpm (27% reduction; P=0.0006). Ivabradine also reduced hospitalizations for any cause (by 15%; P=0.001).

<table>
<thead>
<tr>
<th>End Point</th>
<th>Placebo</th>
<th>Ivabradine</th>
<th>Hazard Ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>First hospitalization</td>
<td>514 (16%)</td>
<td>672 (21%)</td>
<td>0.75 (0.65-0.87)</td>
<td>P&lt;0.001</td>
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<tr>
<td>Second hospitalization</td>
<td>189 (6%)</td>
<td>283 (9%)</td>
<td>0.66 (0.56-0.79)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Third hospitalization</td>
<td>90 (3%)</td>
<td>128 (4%)</td>
<td>0.71 (0.54-0.93)</td>
<td>P&lt;0.012</td>
</tr>
</tbody>
</table>

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**Figure 4.** Kaplan-Meier cumulative event curves for different end points in SHIFT.

(A) Primary composite outcome (cardiovascular mortality or heart failure hospitalization), (B) heart failure hospitalizations, and (C) heart failure deaths in the ivabradine and the placebo arms of SHIFT.

**Abbreviations:** CI, confidence interval; CV, cardiovascular; HR, heart rate; SHIFT, Systolic Heart failure treatment with the If inhibitor ivabradine Trial.

and CV hospitalizations (by 16%; \( P = 0.002 \)). These findings are very important for clinical practice as hospital admissions are not only distressing for patients and their families, but they are also harbingers of accelerated disease progression (manifest by increased risk of readmission and death) and the major driver of the economic burden of HF.

**Reduction in the risk of total and CV mortality in patients with HR of 75 bpm and higher**

Patients with higher HR and therefore at higher CV risk will have the most benefits from HR reduction with ivabradine. The effect of ivabradine was also assessed in the high-risk SHIFT patients (HR ≥75 bpm). The results of this analysis show that in patients with baseline HR ≥75 bpm, ivabradine significantly reduces all clinical outcomes, including the composite primary end point of CV death or hospitalization for HF by 24% (\( P < 0.0001 \)), all-cause death by 17% (\( P = 0.0109 \)), CV death by 17% (\( P = 0.0166 \), death from HF by 39% (\( P = 0.006 \)), and hospitalization for HF by 30% (\( P < 0.0001 \)) (Figure 6). Only 17 patients need to be treated with ivabradine for 1 year to prevent 1 primary outcome, 19 patients to prevent 1 hospitalization for HF, 52 patients to prevent 1 CV death, and 51 patients to prevent 1 all-cause death. Risk reduction with ivabradine was related to both HR level achieved and magnitude of HR reduction. Patients achieving a HR <60 bpm or a HR reduction of more than 10 bpm had the best prognosis. The exceptional benefits of ivabradine in the population with HR ≥75 bpm led the European Medicine Agency to grant a new indication for symptomatic patients with CHF and HR ≥75 bpm.

**Reduction in the risk of major outcomes related to HF whatever the background treatment**

The SHIFT trial has demonstrated a beneficial prognostic effect of ivabradine in the population receiving contemporary HF treatments, including a high rate being prescribed angiotensin-converting enzyme (ACE) inhibitors and/or angiotensin receptor blockers and β-blockers.

The special analysis evaluated whether the dose of background β-blocker therapy had an impact on the effect of ivabradine in the SHIFT population. After adjusting for the previously identified interaction between baseline HR and the effect of treatment with ivabradine, there was no evidence of a trend for differing effect of ivabradine across β-blocker categories (\( P = 0.135 \) for the primary end point, \( P = 0.19 \) for hospital admission for worsening HF, and \( P = 0.30 \) for CV death). This analysis indicates that magnitude of HR reduction with ivabradine beyond what is achieved by a β-blocker, rather than the dose of background β-blocker therapy itself, primarily determines subsequent outcome.

Another analysis assessed the effect of ivabradine in SHIFT patients treated by neurohormonal modulation with multiple drugs, including mineralocorticoid receptor antagonists (MRA). The results of this analysis show that the beneficial effect on outcomes observed with ivabradine in the overall SHIFT population is maintained in patients treated with MRAs, with significant reductions in primary composite end point by 18%, death from HF by 27%, hospitalization for HF by 23%, hospitalization for all causes by 14%, and hospitalization for CV cause by 16%.

**Improvement of symptoms and quality of life in patients with HF**

Symptoms and well-being are other important targets for therapy, together with improvement of outcomes. SHIFT found that New York Heart Association (NYHA) class improved in 29.0% of patients treated with ivabradine vs 24.2% in the placebo group (\( P < 0.0156 \)), and patient-reported global assessment improved in 65.9% of patients treated with ivabradine vs 61.3% in the placebo group (\( P < 0.0345 \)) in the overall SHIFT population. Furthermore, a substudy of the SHIFT trial in 1944 patients demonstrated that in parallel to a reduction in outcomes in the SHIFT trial, ivabradine improved health-related QOL (HQOL) in patients with HF, assessed by the spe-

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**Figure 6.** The effect of ivabradine on outcomes in patients with chronic heart failure and resting heart rate ≥75 bpm.

**Abbreviations:** bpm, beats per minute; CI, confidence interval; HF, heart failure.


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<table>
<thead>
<tr>
<th>Outcome</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite end point</td>
<td>0.76</td>
<td>0.68-0.85</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>0.83</td>
<td>0.71-0.97</td>
<td>0.0166</td>
</tr>
<tr>
<td>Hospitalization for worsening HF</td>
<td>0.70</td>
<td>0.61-0.80</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Death from HF</td>
<td>0.61</td>
<td>0.46-0.81</td>
<td>0.0006</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>0.83</td>
<td>0.72-0.96</td>
<td>0.0109</td>
</tr>
<tr>
<td>All-cause hospitalization</td>
<td>0.82</td>
<td>0.75-0.90</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Any cardiovascular hospitalization</td>
<td>0.79</td>
<td>0.71-0.88</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

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Favors ivabradine | Favors placebo
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0.20 0.40 0.60 0.80 1.00 1.20
cific Kansas City Cardiomyopathy Questionnaire (KCCQ). Treatment with ivabradine significantly improved both scores assessed by the KCCQ: the overall summary score (OSS) and the clinical summary score (CSS). The OSS—which includes physical limitation, total symptoms, QOL, and social limitation scores—was 6.7 in the ivabradine group vs 4.3 in the placebo group ($P<0.001$) at 12 months. The CSS—which includes the physical limitation and the total symptom domain scores—was 5.0 with ivabradine vs 3.3 with placebo ($P=0.018$) at 12 months.

The randomized, open, blinded—end point CARVIVA HF study (effect of CARVedilol, IVAbradine or their combination on exercise capacity in patients with Heart Failure) assessed the effect of HR reduction with carvedilol (25 mg twice daily), ivabradine (7.5 mg twice daily), and their combination (12.5/7.5 mg twice daily) on exercise capacity and QOL in 121 HF patients receiving ACE inhibitor at maximal dose. After 3 months of therapy, the NYHA class improved significantly more in patients receiving ivabradine and combination therapy compared with those allocated to carvedilol. Ivabradine alone or in combination was also more effective for improvement in exercise capacity and QOL compared with carvedilol alone.

The results of the recent study suggest that addition of ivabradine to carvedilol improves exercise capacity in patients with CHF compared with carvedilol alone: the change in distance for the 6-minute walking test was $68.3\pm12.7$ meters in the combination arm vs $32.4$ with carvedilol alone ($P<0.05$) (Table I). In addition, the combination of ivabradine with carvedilol resulted in more than twice the number of patients attaining at least half of the carvedilol target dose (80% of patients vs 38% with carvedilol alone) and shortens the duration of carvedilol uptitration (from 2.7 months with carvedilol alone to 1.9 months in the combination arm).

- **Reversing ventricular remodeling in patients with HF**
  Aside from the clinical standpoint, SHIFT also has important pathophysiological implications, demonstrated by the reverse remodeling observed with ivabradine. An echocardiography substudy in 611 patients from SHIFT demonstrated that 8 months of therapy with ivabradine resulted in a $7 \text{mL/m}^2$ reduction in LV end-systolic volume index (LVESVI), as compared with 0.9 mL/m$^2$ in the placebo group. The LV end-diastolic volume index (LVEDVI) was also reduced by 7.9 mL/m$^2$ as compared with 1.8 mL/m$^2$ in the placebo group; LVEF was improved by 2.4%, whereas there was no change at all in the placebo group. Moreover, these results occurred despite treatment with β-blockers and renin-angiotensin-aldosterone system (RAAS) antagonists, each used in more than 90% of patients.

Reversal of LV remodeling has important clinical implications, as cardiac remodeling is a central feature in the progression of HF and is an established prognostic factor in HF patients. The beneficial impact of ivabradine on LV remodeling and function may contribute to the reduction in cardiac morbidity and mortality found in HF patients treated with ivabradine.

- **Improvement in major outcomes in a wide range of patients with LVSD**
  The recent analysis in the large pooled population of nearly 12 000 patients from BEAUTIFUL and SHIFT trials with LVSD and HR $\geq 70$ bpm demonstrated that ivabradine substantially reduced risk for major outcomes in the broad population of patients with LVSD, whatever the primary clinical presentation (CAD or HF) or clinical status (NYHA class). The results show that ivabradine substantially lowers the risk of major outcomes: the risk of CV death or hospitalization for HF (SHIFT primary end point) decreased by 13% ($P<0.001$), the risk of CV death or hospitalization for HF or MI (BEAUTIFUL end point) decreased by 15% ($P<0.001$), the risk of hospitalization for HF decreased by 19% ($P<0.001$), and the risk of hospitalization for MI decreased by 23% ($P=0.009$). Patients with HR $\geq 75$ bpm, the magnitude of risk reduction with ivabradine was more pronounced, including a 12% reduction in CV mortality ($P=0.049$) and an 11% reduction in total mortality ($P=0.048$). Moreover, the improvement in outcomes observed with ivabradine was not confined to the most severe, symptomatic patients with the worst outcomes, but was observed in patients with less severe profiles as well (eg, LVEF $\leq 40\%$ and NYHA class $\geq I$). Ivabradine was well tolerated with a low rate of symptomatic (4%) or asymptomatic bradycardia (4%), leading to withdrawal in less than 0.9% of patients.

### Table I. Addition of ivabradine to carvedilol in patients with chronic heart failure resulted in a better exercise capacity, shorter β-blocker uptitration period and higher final β-blocker dose. *P<0.05.

<table>
<thead>
<tr>
<th></th>
<th>Carvedilol</th>
<th>Carvedilol + ivabradine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients at ≥50% of carvedilol target dose, n (%)</td>
<td>8 (38%)</td>
<td>16 (80%)*</td>
</tr>
<tr>
<td>Duration of carvedilol uptitration, mo</td>
<td>2.7±0.7</td>
<td>1.9±0.5*</td>
</tr>
<tr>
<td>Final dose of carvedilol, mg/d</td>
<td>29.6±6.2</td>
<td>37.4±8.4*</td>
</tr>
<tr>
<td>∆ HR, bpm</td>
<td>7.2±2.4</td>
<td>12.9±3.5*</td>
</tr>
<tr>
<td>∆ Distance in the 6-min walking test, m</td>
<td>32.4±11.7</td>
<td>68.3±12.7*</td>
</tr>
</tbody>
</table>

**Abbreviations:** bpm, beats per minute; HR, heart rate; n, number.


**Good tolerability profile and easy use in practice**
Throughout its entire clinical development program, ivabradine has always been found to have a good safety profile consistent with its highly specific and selective mode of action on the $I_f$ current. Ivabradine fully preserves the main electrophysiological parameters, including the refractory period of the atrium, atrioventricular conduction time, and repolariza-
tion duration. The absence of changes in the corrected QT interval throughout the follow-up period provides strong evidence of the lack of any significant direct effects of ivabradine on the duration of ventricular repolarization, indicating absence of any proarrhythmic action. In some patients, ivabradine can induce visual symptoms, mainly phosphenes, related to the inhibition of the If current in retinal hyperpolarization-activated and cyclic nucleotide–gated (HCN) channels. They were generally mild and well tolerated, resolving spontaneously during or after treatment, and leading to withdrawal in less than 1% of patients without safety concern.

Bradyarrhythmia was reported in 2.2% of patients with angina treated with ivabradine 7.5 mg twice daily compared with 4.4% with atenolol 100 mg once daily. In HF patients in the SHIFT trial, bradyarrhythmia led to permanent withdrawal from the study in only 1% of patients on ivabradine. This low percentage is explained by a clear plateau in the dose-response curve of If current inhibition and by the direct rate-related dynamics of the HR-lowering effect, limiting the risk of excessive bradycardia and ensuring the greatest HR reduction in patients with the highest pretreatment HR.

Achievement of target dose of ivabradine is simple in comparison with other treatments, with titration from 5 mg (starting dose) to 7.5 mg twice daily if HR remains above 60 bpm, which simplifies the management of angina or HF patients. Importantly, the abrupt discontinuation of ivabradine does not result in a rebound phenomenon. The absence of rebound tachycardia with ivabradine not only simplifies the management of antianginal treatment, but also reduces the risk of adverse effects following missed doses or unscheduled gaps in medication administration.

These characteristics of the HR-lowering action of ivabradine make it suitable and simple to use in most symptomatic patients with CAD or HF.

Conclusion

The existing evidence supports ivabradine as an important therapeutic modality to enhance management of patients with CAD or CHF. SHIFT shows ivabradine to be an effective treatment that can fulfill unmet needs in the management of CHF patients: improvement of symptoms and well-being together with outcomes. Due to ivabradine’s beneficial effects on angina symptoms and myocardial ischemia and its ability to prevent coronary events, it is an important agent in the management of patients with angina. The ongoing SIGNIFY trial is assessing the potential of ivabradine to improve prognosis in a large population of patients with stable CAD and HR >70 bpm. The results of this trial will provide new insight into the role of ivabradine in the management of patients with stable CAD.

References

23. Heidenreich PA, Sahay A, Kapoor JR, Fman MX, Massie B. Divergent trends in...


Keywords: coronary artery disease; heart failure, heart rate reduction; I\textsubscript{i} current; ivabradine; Procoralan; sinus node; stable angina

Bénéfices cliniques de Procoralan (ivabradine) : mise en évidence et perspectives

Procoralan (ivabradine), premier inhibiteur sélectif et spécifique du courant I\textsubscript{i}, diminue la fréquence cardiaque (FC) sans modifier la contractilité myocardique, le système de conduction cardiaque ou la résistance vasculaire coronaire. D’après des données expérimentales, la baisse de la fréquence cardiaque par l’ivabradine est spécifique et le mécanisme sélectif qui la sous-tend maximise les bénéfices en améliorant la perfusion coronaire et l’efficacité de la pompe cardiaque. L’ivabradine, en agissant sur les symptômes angineux et l’ischémie myocardique et en prévenant les événements coronaires, est un élément essentiel de la prise en charge des patients coronariens. En raison de ses propriétés cliniques et pharmacologiques, l’ivabradine est un traitement de fond pour les insuffisants cardiaques chroniques (ICC). D’après les résultats de l’étude SHIFT (Systolic Heart failure treatment with the I\textsubscript{i} inhibitor ivabradine Trial), l’ivabradine répond particulièrement bien aux besoins thérapeutiques insatisfaits des ICC, en améliorant les symptômes et le bien-être, ce qui pose son importance dans l’amélioration de la prise en charge des patients atteints de MC ou d’ICC. L’étude en cours SIGNIFY (Study assessmentG the morbidity-mortality beNefits of the I\textsubscript{i} inhibitor ivabradine in patients with coronary artery disease) cherche à proposer un nouveau paradigme thérapeutique en supposant que la réduction de la FC améliore les résultats cliniques à long terme des patients coronariens stables sans IC clinique. Les résultats devraient nous éclairer sur le rôle de l’ivabradine dans la prise en charge des patients coronariens stables.
Coronary artery disease (CAD) remains the leading cause of death worldwide, despite tremendous progress toward the prevention and cure of cardiovascular (CV) diseases. Thus, any insight into how to improve care and outcomes in CAD patients is of tremendous value both to patients and public health. Reducing risk factors to prevent atherosclerotic events is important in CAD management. An easily modifiable parameter to improve risk management in patients with CV disease is resting heart rate (HR), and reducing HR is a well-recognized strategy for ischemia prevention in CAD patients. Reducing resting HR may also have an impact on long-term outcomes. Much evidence from experimental and clinical studies suggests that elevated resting HR predisposes for development and progression of atherosclerosis and plaque rupture, which can trigger the acute coronary events linked to mortality in CAD patients. Consistent with the important role of HR in the pathophysiology of CAD, HR reduction should be considered a key therapeutic goal in CAD patients. The ongoing SIGNIFY trial (Study assessing the morbidity-mortality benefits of the I inhibitivabradine in patients with coronary artery disease) is assessing if lowering resting HR with ivabradine improves outcomes in patients with stable CAD without clinical heart failure (HF) and who are receiving appropriate CV treatment. If ivabradine reduces CV morbidity and mortality in such patients, this trial would constitute a breakthrough in treatment strategies for stable CAD patients, allowing us to reach both treatment goals: CV-event prevention and symptom reduction, improving quality of life.

Medicographia. 2013;36:98-102 (see French abstract on page 102)

What is the rationale and the objective of the SIGNIFY trial?

Coronary artery disease (CAD) is the leading cause of death worldwide and is predicted to remain so for the next 20 years. For these reasons, any insight into how to improve care and outcomes in patients with CAD is of tremendous value to patients as well as to public health. Reduction of risk factors to prevent atherosclerotic events is important for the management of CAD. One easily modifiable parameter that could improve risk management in patients with cardiovascular (CV) disease is resting heart rate, and HR reduction is a well-recognized strategy for ischemia prevention in patients with CAD. By reducing myocardial work and myocardial oxygen consumption and by increasing diastolic filling time and myocardial oxygen supply, HR reduction minimizes the pathophysiological substrate of angina. Reduction in resting HR may also have an impact on long-term outcomes. The
investigators of the BEAUTIFUL (morBidity-mortality EvAlUaTion of the I f inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction) trial have contributed substantially to the understanding of the prognostic importance of elevated HR by prospective evaluation of the impact of high resting HR on outcomes in patients with stable CAD and left ventricular systolic dysfunction (LVSD). The prospective analysis of data from the placebo arm demonstrated that elevated resting HR (≥70 beats per minute [bpm]) is a strong independent predictor of clinical outcomes. A large body of evidence from experimental and clinical studies suggests that elevated resting HR predisposes to development and progression of atherosclerosis and plaque rupture, which can trigger the acute coronary events that are linked to mortality in patients with CAD. Elevated HR enhances the magnitude and frequency of the tensile stress imposed on the arterial wall and prolongs exposure of coronary endothelium to systolic low and oscillatory shear stress, which modulates endothelial gene expression through complex mechanoreception and mechanotransduction processes, inducing an atherogenic endothelial phenotype and formation of an early atherosclerotic plaque. All these processes induce structural and functional changes of the endothelial cells, leading to endothelial dysfunction, and make the endothelium more permeable to circulating low-density lipoprotein (LDL) and inflammatory cells, facilitating entry into the intima. Besides the implication of increased HR in atherogenesis, it may also promote weakening of the fibrous cap, ultimately increasing the risk of plaque disruption and the onset of acute coronary syndrome. Consistent with the important role of HR in the pathophysiology of CAD, HR reduction should be considered a key therapeutic goal in CAD patients. We designed the SIGNIFY trial (Study assessInG the morbidity-mortality beNefits of the I f inhibitor ivabradine in patients with coronary artery disease) to test the hypothesis that lowering resting HR with ivabradine would improve outcomes in patients with stable CAD without clinical heart failure (HF) and who are receiving appropriate CV treatment.

What is the rationale for ivabradine treatment in patients with stable CAD?

Ivabradine is a HR-lowering agent that reduces HR selectively by inhibiting the sinoatrial pacemaker If current and thereby decreases HR without having any direct effect on other cardiac functions. Existing evidence on prevention of myocardial ischemia and coronary and HF-related events make it an important agent in current management of patients with CAD as well as HF. Ivabradine has been proven effective for prevention of myocardial ischemia and treatment of symptoms in patients with chronic stable angina pectoris. In head-to-head comparisons, its anti-ischemic and antianginal effectiveness was comparable to such established drugs as a β-blocker and a calcium channel blocker. The ASSOCIATE trial (evaluation of the Antianginal efficacy and Safety of the aSsociATion Of the If Current Inhibitor ivAbradine with a beTa-blockEr) shows that ivabradine further reduces HR and improves exercise capacity, while being well tolerated when added to long-term treatment with β-blockers. The BEAUTIFUL trial (morBidity-mortality EvAlUaTion of the I f inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction) suggested further benefits of ivabradine in prevention of coronary outcomes in patients with stable CAD and LVSD with an elevated resting HR of ≥70 bpm (n=5392): ivabradine significantly reduced admission to hospital for myocardial infarction (MI) (relative risk reduction [RRR], 36%; P=0.001), admission to hospital for MI or unstable angina (RRR, 22%; P=0.023), as well as coronary revascularization (RRR, 30%; P=0.016). In patients whose limiting symptom at baseline was angina (n=1507), ivabradine reduced the composite of CV mortality or hospitalization for fatal and nonfatal MI or HF by 24%. Therapy with ivabradine resulted in a 42% reduction in the risk for hospitalization for fatal and nonfatal MI in all patients with limiting angina and 73% reduction in those with resting HR of 70 bpm and higher. Recent SHIFT (Systolic Heart failure treatment with the I f inhibitor ivabradine Trial) results showing statistically significant and substantial reductions in CV death or HF hospitalization as well as in HF deaths in patients with chronic HF have significantly extended the range of clinical benefits of ivabradine to patients with HF. The recent meta-analysis in the large pooled population of near-
ly 12 000 patients from BEAUTIFUL and SHIFT trials demonstrated that ivabradine substantially reduces risk for major outcomes in the broad population of patients with LVSD and a HR ≥70 bpm, whatever the primary clinical presentation (CAD or HF) or clinical status (New York Heart Association [NYHA] class). So, the ongoing SIGNIFY trial is a logical extension of the clinical program and is testing the hypothesis that HR lowering with ivabradine reduces CV-event rates in patients with stable CAD without clinical HF.

What is the design of the SIGNIFY trial?

SIGNIFY is a randomized, double-blind, placebo-controlled, multicenter trial in patients with stable CAD without clinical HF, with 2 parallel and balanced treatment arms. It is designed to demonstrate the superiority of ivabradine over placebo in the reduction in CV mortality or nonfatal MI (composite end point).

Following a run-in period of 14 to 30 days, patients will be randomized to the active double-blind treatment period (ivabradine versus placebo). Consistent with current recommendations, the target HR should be 55-60 bpm. Since the patients included in this trial are clinically stable patients with elevated HR (≥70 bpm), the starting dose of ivabradine is 7.5 mg bid, with the possibility to increase to 10 mg bid after 1 month (according to the patient’s HR and the presence or absence of signs and symptoms likely to be due to bradycardia). Currently, up titration of ivabradine is recommended up to 7.5 mg bid. The range of ivabradine doses selected for this study has been chosen based on the range of ivabradine doses used in the patients with CAD and stable angina involved in the development program of ivabradine. The primary objective is to assess whether lowering resting HR with ivabradine reduces CV mortality or nonfatal MI (composite end point). The secondary objectives are to assess the effect of ivabradine compared with placebo on all-cause mortality, CV mortality, nonfatal MI, coronary revascularization, new-onset or worsening HF, as well as some composite coronary end points. In addition, the effect of ivabradine on quality of life and angina symptoms will be assessed in patients with angina symptoms at baseline.

What is the study population?

We designed the inclusion and exclusion criteria to identify a group of patients aged 55 years or older with stable CAD and without clinical HF (LV ejection fraction >40%) at sinus rhythm, with resting HR equal to or higher than 70 bpm, and who are receiving appropriate medications to treat their CV conditions. They should also have at least 1 major risk factor such as angina symptoms (Canadian Cardiovascular Society [CCS] class II or higher), or objective evidence of myocardial ischemia induced by stress testing within the previous 12 months, or recent hospitalization for a major coronary event (acute MI or unstable angina) within the previous 12 months; or 2 minor CV risk factors such as low high-density lipoprotein (HDL) cholesterol and/or high LDL cholesterol, treated diabetes mellitus, presence of peripheral artery disease, current smoking, or age over 70 years.

What is the prognosis of patients with stable CAD?

Patients with stable CAD have high event rates despite modern treatments. The prognosis in patients with chronic CAD depends on several factors, including underlying coronary anatomy, left ventricular function, the presence of risk factors, and comorbidities. The data from the large REACH registry (REduction of Atherothrombosis for Continued Health) in stable CAD outpatients (n=38 602 patients) have confirmed that among patients with CV disease, those with established stable CAD had the highest nonfatal MI rate and the highest nonfatal stroke rate. The registry reported annual event rates of 15.2% for death, stroke, MI, or hospitalization for an atherothrombotic event; and also 6.4% for unstable angina; 4.5% for death, acute MI, and stroke; and 3.8% for revascularization by percutaneous coronary intervention. Thus, approximately 3 out of 20 patients with established CAD had a major event or had been hospitalized within a year of follow-up. The data from the Heart and Soul Study demonstrated that during a mean of 3.9 years, coronary events (MI or CAD death) occurred in 7% of participants without angina or inducible ischemia, 10% of those with angina alone, 21% of those with inducible ischemia alone, and 23% of those with both angina and inducible ischemia.

The most recent data from the ongoing registry CLARIFY (prospective observational Longitudinal Registry of patients with stable coronary artery disease), which enrolled more than 33 000 patients with stable CAD in 45 countries, showed that the 1-year event rate of the composite of CV death, nonfatal MI, or stroke was similar for men and women (1.7% and 1.8%, respectively), all-cause death was 1.5% and 1.6%; and CV death or nonfatal MI was 1.4%. These data from the well-treated population from this large, stable, contemporary outpatient cohort with established CAD indicate that continued efforts are needed to improve secondary prevention and clinical outcomes.

What is the optimal HR in stable CAD patients and how is it achieved in clinical practice?

Consistent with the important role of elevated HR in the pathophysiology of myocardial ischemia, it is recommended to reduce resting HR to 55-60 bpm in stable coronary patients as well as in the acute coronary setting. Thus, current American College of Cardiology (ACC)/American Heart Association (AHA) guidelines for the diagnosis and management of patients with stable CAD recommended that β-blocker dosing be adjusted to limit the HR to 55-60 bpm. It is stressed that this is important not only for effective prevention...
of angina, but also due to the prognostic importance of HR. A new analysis from the TNT trial (Treating to New Targets) in 9602 patients with established CAD evaluated the optimal HR level regarding the risk of CV events. In patients with CAD, the relationship between HR and outcomes follows a J-curve pattern. This analysis identified a nadir of 52.4 bpm associated with the lowest event rate for the primary end point of death from CAD, nonfatal MI, resuscitated cardiac arrests, and fatal or nonfatal stroke. There was no target-organ heterogeneity and the nadir was similar for all outcomes, indicating that a target range of 50-59 bpm is optimal for the best prognosis in patients with CAD.

The existing evidence suggests that a HR of 55-60 bpm might be considered optimal for both ischemia prevention and, perhaps, prevention of CV events. However, despite the recommendation to reduce HR to 55-60 bpm, resting HR is not controlled in a significant proportion of patients in clinical practice. Many surveys conducted in coronary patients revealed low rates of HR control. For example, in the European Heart Survey of patients with stable angina, mean resting HR was 73 bpm. The most recent data from the CLARIFY registry are consistent with this observation and show that only 22% of patients with angina achieved a HR of <60 bpm.

These data show that there is a lot of room for improvement in HR control and therefore considerable potential to improve management of stable CAD patients. The ongoing SIGNIFY trial is testing whether lowering HR with ivabradine represents a new therapeutic opportunity to improve prognosis for a large population of patients with stable CAD.

When do you expect the results and how might they advance the management of patients with stable CAD?

The recruitment period was from October 2009 to April 2012. Today [as of May 2012], SIGNIFY has recruited 19 102 patients. We expect to have the results by the end of 2014. These data will be extremely important for clinical practice, as taking into account the prevalence and burden of CAD, any further strategy into how to improve care and outcomes in patients with CAD is of tremendous value to patients as well as to public health. Resting HR is a potentially modifiable CV risk factor and, therefore, HR lowering provides great therapeutic opportunity to reduce mortality and CV events in patients with stable CAD. The SIGNIFY study aims to extend the evidence on prognostic benefits of HR reduction with ivabradine to patients with CAD without HF. BEAUTIFUL suggested that ivabradine improves the coronary event rate in patients with stable CAD and LVSD with a HR of 70 bpm or higher. Other antianginal strategies either have never been tested or failed to demonstrate the benefits on CV events in stable CAD patients. The evidence for β-blocker use is derived from relatively old post-MI studies, most of which antedate modern reperfusion or medical therapy, and from HF trials, but has been widely extrapolated to all patients with CAD. However, the long-term efficacy of these agents in patients treated with contemporary medical therapies is not known, even in patients with prior MI.

The recently published analysis from the REACH registry assessed whether the use of β-blockers is associated with reduction in CV events in patients with a prior history of MI, in those with CAD without MI, and in those with only risk factors for CAD in a large contemporary population of 21 860 patients included in the propensity score–matched analysis (median follow-up was 44 months). The results showed that despite the perception that β-blockers are beneficial in all stable CAD patients, their use in an era of modern medical and reperfusion therapy in stable CAD patients was not associated with lower CV-event rates. This finding raises questions regarding the need for long-term use of β-blockers in patients 1 year after MI or in those who had percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) without MI. These data also suggest the importance of and need for randomized trials in this era of modern medical and reperfusion therapy to identify the optimal therapy in stable CAD. So, if the results show that ivabradine treatment reduces CV morbidity and mortality in patients with stable CAD and preserved LV function, this trial will constitute a breakthrough in treatment strategies for stable CAD patients, allowing us to reach both of our goals when treating such patients: CV-event prevention and symptom reduction, improving quality of life.
SIGNIFY : un espoir de nouvelles perspectives dans la prise en charge de la MC

Malgré des progrès considérables dans la prévention et le soin des maladies cardio-vasculaires (CV), la maladie coronaire (MC) reste la principale cause de décès dans le monde. Toute information concernant l’amélioration des soins et l’évolution des patients coronariens est donc capitale pour les patients et la santé publique. Il est important, dans la prise en charge de la MC, de réduire les facteurs de risque pour prévenir l’athérosclérose. La fréquence cardiaque (FC) de repos est un paramètre facilement modifiable pour améliorer la prise en charge du risque chez les patients coronariens. La réduction de la FC de repos peut aussi avoir un impact sur l’évolution à long terme. De nombreuses données issues d’études cliniques et expérimentales montrent une FC de repos élevée prédit au développement et à la progression de l’athérosclérose et de la rupture de plaque, ce qui peut déclencher des événements coronaires aigus, cause de mortalité chez les patients coronariens. Eu égard au rôle important de la FC dans la physiopathologie de la MC, sa réduction doit être considérée comme un objectif thérapeutique clé chez les patients coronariens. L’étude en cours SIGNIFY (Study assessInG the morbidity-mortality beNefits of the I$_{i}$ inhibitor ivabradine in patients with coronary artery disease) cherche à évaluer si la baisse de la FC de repos avec l’ivabradine améliore l’évolution des patients coronariens stables sans insuffisance cardiaque (IC) et qui reçoivent un traitement CV approprié. Si l’ivabradine réduit la morbidité et la mortalité CV chez de tels patients, cette étude constituerait un progrès décisif pour les stratégies thérapeutiques des patients coronariens stables, permettant d’atteindre deux buts principaux : la prévention des événements CV et la réduction des symptômes, et donc l’amélioration de la qualité de vie.
Molecular imaging combines imaging modalities to assess plaque morphology, perfusion, and metabolism/inflammation. From a clinical standpoint, the combination of positron emission tomography, which uses a radiolabeled tracer capable of visualizing molecular targets in the picomolar range, and computed tomography angiography, which has excellent spatial and temporal resolution, figures prominently among the current most advanced modalities.

This short review discusses the implications of findings from recent clinical studies on the use of invasive and noninvasive imaging modalities in the detection of high-risk coronary lesions. Based on findings from autopsy studies, a short summary of the morphological features of coronary plaques responsible for acute coronary events is provided, and the concept of the “vulnerable plaque” is outlined. With regard to invasive imaging of the coronary vasculature, a focus is given to intravascular ultrasound, with discussion of recent prospective data on the morphology and progression of coronary plaques and their correlation with plaque rupture. Advances in optical coherence tomography are also illustrated in relation to defining the features of unstable plaques. Among the noninvasive imaging modalities, a focus is placed on computed tomography coronary angiography for identification of the morphological characteristics of coronary plaques that correlate with future coronary events. In addition, the prospects for magnetic resonance imaging and molecular hybrid imaging are outlined. Among the latter, combined positron emission tomography/computed tomography angiography is emerging as a prominent modality that enables characterization of both the morphology and biology of coronary plaques in patients. Finally, the place of imaging modalities alongside the currently available clinical risk scores and biomarkers for identification of individuals at risk for future coronary events is discussed, in addition to how these may guide therapeutic management.

Plaque rupture or erosion (or more rarely, calcific nodules) with ensuing atherothrombosis constitutes the underlying pathophysiology of acute coronary syndromes (ACS). The pathomorphological features of ruptured plaques comprise a thin fibrous cap, a large lipid core, outward (positive) remodeling, angiogenesis, and an abundance of inflammatory cells. Thin-cap fibroatheroma (TCFA) by definition comprises a large necrotic core covered by a thin fibrous cap of <65 μm. It is typically found in the proximal segments of coronary arteries with less than 50% diameter stenosis, and represents the most frequent type of lesion found in patients dying of coronary plaque rupture.

By inference, when plaque composition is characteristic of a ruptured plaque, but there is an intact fibrous cap remaining, it is considered to predispose the “vulnerable plaque” to rupture. The natural course of coronary plaques with features of vulnerable plaque is not unidirectional, and it does not always involve a move toward...
plaque rupture manifesting as ACS, but rather it often remains asymptomatic, with ruptured plaques healing. The advent of novel imaging modalities has enabled detailed analysis of the natural course of vulnerable plaques and its correlation with clinical events.

**Invasive imaging modalities for assessment of high-risk coronary plaques**

For decades, coronary angiography constituted the primary invasive imaging modality for assessment of the presence and degree of luminal stenosis (quantitative coronary angiography; QCA). Particularly when combined with pressure wire measurements, the modality enables quantitative evaluation of the functional relevance of myocardial perfusion and the risk for future cardiovascular events. Although QCA improved the quantification of coronary lesions, the fact that it is based on only 2 projections of a 3-dimensional structure means that it nevertheless has limitations. On the other hand, the assessment of fractional flow reserve has made it possible to precisely quantify the hemodynamic relevance of coronary lesions (for a review see reference 6).

Grayscale intravascular ultrasound (IVUS) enables visualization of vessel size, plaque burden, and morphology at a resolution of 100 μm to 120 μm by means of amplitude analysis of backscattered sound waves. In contrast to IVUS, coronary angiography grossly underestimates the extent of plaque burden and outward expansion of the atheromatous arterial wall (positive remodeling). Radiofrequency IVUS (RF-IVUS, virtual histology) allows for enhanced assessment of plaque composition, and results correlate well with histology findings. The prospective multicenter PROSPECT study (Providing Regional Observations to Study Predictors of Events in the Coronary Tree), an imaging study in patients with unstable atherosclerotic lesions, evaluated the morphological characteristics of nonculprit lesions and their progression over time, as well as their association with future cardiovascular events, using grayscale IVUS and RF-IVUS versus coronary angiography. After 3 years, cardiovascular events were reported in 20.4% of patients, and were associated in equal measure with nonculprit lesions and culprit lesions that had previously been treated by percutaneous coronary intervention (PCI) at the time of ACS. Nonculprit lesions associated with cardiovascular events were characterized by a plaque burden of ≥70%, a minimal lumen area of ≤4 mm², and TCFA, the latter defined by RF-IVUS. Interestingly, nonculprit lesions associated with future events were classified angiographically as baseline as mild stenotic lesions, indicating that identification of patients at risk for future events using coronary angiography alone is limited. In turn, nonculprit lesions with angiographically mild stenosis, but a high plaque burden (>70%), were found in one-third of patients and were more frequent in patients with diffuse coronary artery disease (CAD) (3-vessel disease) and a prior history of PCI, demonstrating the systemic nature of atherosclerosis as the underlying disease. However, it should be noted that of the 74 events that occurred in nonculprit vessels, 67 were related to revascularization procedures for progressive or unstable angina. There were no deaths or cardiac arrests and only 6 myocardial infarctions in nonculprit vessels during follow-up, highlighting the overall low event rates achieved with current medical prevention strategies. Grayscale IVUS has consistently been used to demonstrate slowing of coronary plaque progression, and even regression following statin therapy. Thus, IVUS is a useful tool to assess the effects of pharmacotherapy on plaque stabilization. Recently, a pooled analysis was carried out of 7 trials involving performance of serial IVUS measurements at baseline and after 21 months to assess the effects of various pharmacotherapies. The analysis identified smaller minimal lumen area, greater plaque burden at baseline, and greater progression of atheroma volume and constrictive arterial remodeling in the left main coronary artery (LMCA) as predictors of cardiovascular events. Interestingly, the response to treatment in the LMCA was opposite that in other vascular territories of the coronary tree, and it remains unclear as to how this impacts on risk prediction for future events. Furthermore, in a recent prospective multicenter trial, IVUS-based identification of a minimum lumen area of 6 mm² as a cutoff value to guide revascularization of intermediate LMCA plaques did not translate into a difference in the rate of future events within 2 years.

Optical coherence tomography (OCT) is based on infrared light emitted from a catheter-based light source, and has better resolution (10 μm to 15 μm), but less penetration than IVUS enabling clear visualization of the intima and differ-

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**Selected abbreviations and acronyms**

<table>
<thead>
<tr>
<th>ACS</th>
<th>acute coronary syndromes</th>
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<tbody>
<tr>
<td>CAC</td>
<td>coronary artery calcium</td>
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<tr>
<td>CAD</td>
<td>coronary artery disease</td>
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<tr>
<td>CT</td>
<td>computed tomography</td>
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<tr>
<td>CTCA</td>
<td>computed tomography angiography</td>
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<td>FDG</td>
<td>fluorodeoxyglucose</td>
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<td>GRACE</td>
<td>Global Registry of Acute Coronary Events</td>
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<tr>
<td>IVUS</td>
<td>intravascular ultrasound</td>
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<tr>
<td>LMCA</td>
<td>left main coronary artery</td>
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<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
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<tr>
<td>NSTEMI</td>
<td>non-ST-segment elevation myocardial infarction</td>
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<tr>
<td>OCT</td>
<td>optical coherence tomography</td>
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<tr>
<td>PCI</td>
<td>percutaneous coronary intervention</td>
</tr>
<tr>
<td>PET</td>
<td>positron emission tomography</td>
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<tr>
<td>PROSPECT</td>
<td>Providing Regional Observations to Study Predictors of Events in the Coronary Tree</td>
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<tr>
<td>QCA</td>
<td>quantitative coronary angiography</td>
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<tr>
<td>RF</td>
<td>radiofrequency</td>
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<tr>
<td>SCORE</td>
<td>Systematic COronary Risk Evaluation</td>
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<tr>
<td>TCFA</td>
<td>thin-cap fibroatheroma</td>
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<tr>
<td>TIMI</td>
<td>Thrombolysis in Myocardial Infarction</td>
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Frequency domain (FD) OCT constitutes a refinement of the time-domain technology of OCT, enabling a faster pull-back during imaging, reducing the time needed for flushing of blood from the lumen and thus providing better image quality and improved handling of this technique. Due to its excellent imaging quality in the near field, the main application of this technique is currently visualization of stent coverage and assessment of stent apposition and intimal dissection in the evaluation of the vascular response to stent implantation in interventional cardiology. Furthermore, FD OCT can be used to visualize plaque morphology such as fibrous cap thickness, the lipid core, calcium, plaque rupture, and thrombus apposition (including atherosclerotic plaques in bypass grafts, as shown in Figure 2), and even macrophage

Figure 1. Intravascular imaging modalities for the assessment of coronary plaque. 

Figure 2. Thrombus in a venous bypass graft adjacent to atherosclerotic plaque. 
(A) Coronary angiogram with thrombus in saphenous vein graft (arrowhead), (B) Frequency domain optical coherence tomography (OCT) with thrombus (arrowhead) and graft atherosclerotic plaque with a large lipid core (white arrows), (C-E) Frequency domain OCT with thrombus (arrowheads), (F) Coronary angiogram after stent deployment.
density and collagen composition of fibrous caps. Early reports indicate that OCT provides better detection of plaque rupture and thrombus in patients with ACS than IVUS and coronary angiography, in addition to defining TCFA. The ability to detect TCFA was found to be better in patients with acute myocardial infarction/ACS than in those with symptomatic stable CAD. Unlike IVUS, OCT is a rather novel technique, and standards for characterization of plaque composition and useful data interpretation need to be defined. In this respect, a recent study involving a systematic comparison of computed tomography (CT) angiography, IVUS, and OCT against histopathological examination ex vivo may set the stage for future studies. For discriminating between early and advanced coronary plaques, diagnostic accuracy was found to be best with OCT, followed by CT angiography and IVUS. Furthermore, by using both OCT (high spatial resolution) and IVUS (high penetration), thus combining the strengths of both methods, it was recently demonstrated that statin therapy increased fibrous cap thickness and decreased plaque and lipid volume indices in patients with CAD.

Noninvasive imaging modalities for assessment of high-risk coronary plaques

Multidetector CT technology enables determination of the coronary artery calcium (CAC) score, which is a measure of total plaque burden in the coronary vasculature. The CAC score is a powerful tool for risk prediction in asymptomatic individuals. However, a high CAC score does not rule out significant coronary stenosis and does not exclude the presence of noncalcified plaques. CT coronary angiography (CTCA) permits delineation of coronary plaque morphology, plaque volume, eccentric remodeling, and the presence of calcifications, and allows a crude assessment of plaque composition based on increasing amounts of calcium (noncalcified, mixed, and calcified plaques). A large plaque area, a high remodeling index, and a relatively large proportion of noncalcified and mixed plaque components on CTCA is found more often in culprit plaques of ACS patients than in patients with stable angina. Moreover, in 1 study, patients who had plaques with signs of positive remodeling and lower CT density had a higher likelihood of developing an ACS during a 2-year follow-up period. Furthermore, addition of plaque composition (≥2 segments with noncalcified plaque) to stenosis severity (≥50%) provided incremental prognostic information to reduced myocardial perfusion in patients with suspected CAD who were evaluated prospectively by CTCA and single-photon emission CT myocardial perfusion imaging. In addition, CTCA enables assessment of the progression of coronary plaques and statin-induced changes in plaque morphology. However, current CTCA analysis of coronary plaques is still limited by the spatial resolution of CTCA, which precludes depiction of TCFA (<65 µm cap thickness), the presumable precursor to plaque rupture. Furthermore, subclassification of noncalcified plaques into predominantly lipid-rich/necrotic versus fibrous plaque based on CT density is still unreliable. A “napkin-ring”–like enhancement of the plaque border surrounding the hypodense core seen on intravascular imaging with OCT and on histopathology examination was recently found to be associated with TCFA (Figure 3) and is thought to represent a sign of plaque vulnerability.

Magnetic resonance imaging (MRI) of the coronary vasculature is an emerging modality driven forward by technological advances that have translated into better temporal resolution, improved signal-to-noise ratio, and reduced scan times. Recent MRI studies have demonstrated positive remodeling of the vascular wall in patients with CAD, and a positive correlation between coronary wall thickness and cardiovascular risk factors and intima-media thickness, but not CAC score. Combining MRI with use of ultrasmall superparamagnetic iron oxide particles allows for visualization of macrophage-rich areas, and thus plaque inflammation, in carotid arteries. A recent
The place of imaging in the diagnostic work-up of individuals at risk for future adverse events

In primary prevention, risk calculators such as the Framingham Risk Score or the Systematic Coronary Risk Evaluation (SCORE) model are widely used. These scores integrate established cardiovascular risk factors to identify high-risk individuals, defined as those with a >20% absolute risk of experiencing a fatal coronary event or a nonfatal myocardial infarction within a 10-year period (Framingham Risk Score) or those with a ≥5% risk of death within a 10-year period (SCORE).

The challenge for the clinician concerning whether to initiate lifestyle changes and/or therapy lies in the identification of individuals in the intermediate-risk group. A recent analysis of a large cohort of asymptomatic individuals identified CAC as an independent predictor of future cardiovascular events in intermediate-risk individuals, as measured by CT. CAC provided superior discrimination and risk reclassification compared with other risk markers, including C-reactive protein. At present, it is unclear whether imaging of plaque morphology and biology that goes beyond the determination of CAC can translate into even better discrimination of individuals at risk and, most importantly, help guide the decision as to when to initiate therapy in asymptomatic individuals.

In the setting of ACS, commonly-used risk scores are the Thrombolysis in Myocardial Infarction (TIMI) risk score for patients with unstable angina/non-ST-segment elevation myocardial infarction (NSTEMI) and ST-segment elevation myocardial infarction (STEMI), and the Global Registry of Acute Coronary Events (GRACE) risk score, which covers the whole spectrum of ACS. Compared with the clinical TIMI risk score alone, addition of a highly sensitive troponin test to the TIMI risk score resulted in improved risk stratification of patients with NSTEMI. Despite the impact of PROSPECT in defining with the use of RF-IVUS morphological characteristics of coronary plaques that are associated with future cardiovascular events, the study did not provide any answers concerning lesions that are not TCFAs, but that also cause ACS in the absence of plaque rupture, ie, in the presence of plaque erosion and calcific nodules. Future studies are needed to address whether RF-IVUS-based identification of nonculprit lesions in patients with ACS can guide interventional/pharmacological strategies to prevent future events. Furthermore, prospective studies assessing the morphological characteristics and progression over time of nonculprit lesions and their association with future cardiovascular events with the use of OCT versus coronary angiography are lacking. Moreover, studies that address the impact of interventions on outcome after OCT identification of vulnerable plaques are clearly needed. Among the noninvasive imaging modalities, CT angiography appears the most clinically advanced, but identification of the most appropriate population to screen for coronary plaque morphology in order to prevent future ACS remains to be addressed in future studies. Similarly, following successful proof-of-concept studies using FDG-PET/CT angiography, prospective studies are needed to evaluate whether vulnerable plaques can therefore be identified prior to any clinical manifestation, and there is also a need to minimize radiation exposure with these modalities.

In summary, despite having a prominent place in the identification of coronary plaques that show characteristics of vulnerability, prospective data are only now beginning to emerge regarding the value of these imaging modalities in helping to guide therapies.

References

108 MEDICOGRAPHIA, Vol 36, No. 1, 2014

Imaging of vulnerable plaques – Lüscher and others
Ce court article analyse les conséquences des résultats d’études cliniques récentes sur l’utilisation de l’imagerie invasive et non invasive dans la détection des lésions coronaires à haut risque. Nous résumons rapidement d’après les résultats d’études d’autopsie, les différents traits morphologiques des plaques coronaires responsables d’événements coronaires aigus et nous présentons le concept de « plaque vulnérable ». L’imagerie du réseau coronarien étant invasive, nous nous intéressons particulièrement à l’échographie intravasculaire en discutant les données prospectives récentes sur la morphologie et la progression des plaques coronaires et leur corrélation avec la rupture de plaque. Nous illustrons également les progrès de la tomographie par cohérence optique dans l’identification des caractéristiques des plaques instables. Parmi les techniques d’imagerie non invasive, la coronarographie par tomodensitométrie se distingue dans l’identification des spécificités morphologiques des plaques coronaires en relation avec de futurs événements coronaires. De plus, nous résumons les perspectives de l’imagerie par résonance magnétique et de l’imagerie hybride. Parmi cette dernière, la tomographie par émission de positrons couplée à l’angioscanner représente un moyen de premier plan pour préciser la morphologie et la biologie des plaques coronaires. Enfin, nous analysons parallèlement la place des techniques d’imagerie et celle des scores cliniques de risque et des biomarqueurs actuellement disponibles pour identifier les patients à risque d’événements coronaires ainsi que leur capacité à guider la prise en charge thérapeutique.

**Keywords:** coronary artery disease; high-risk coronary lesion; invasive imaging; noninvasive imaging; risk stratification
Benjamin Franklin (1706-1790), a Founding Father of the United States of America, loved France, and was hugely popular there. A French wine connoisseur, he kept more than a thousand bottles in his Parisian cellar. A hit with the ladies in town and at court, his experiments on electricity drew enthusiastic crowds, he helped debunk Franz Anton Mesmer's claims about magnetism, and contributed major medical inventions and insights. The public attention fawned on him did not distract him from his diplomatic duties, and as first ambassador to France he drafted two vital treaties for the fledgling American nation, in 1778 and 1783. Learn more as historians Thomas Fleming and Jan Hirschmann tell us about Franklin in France and as a scientist.

Taking Paris by storm:

**Benjamin Franklin**, American Founding Father and first ambassador to France

**T. J. Fleming, USA**

Page 112

Dr **Benjamin Franklin**’s scientific and medical legacy

**J. V. Hirschmann, USA**

Page 123
A full year and a half before the Declaration of Independence, Benjamin Franklin demonstrated his ability to speak for the American people. It made perfect sense for the members of the Continental Congress to turn to Franklin to seek the help they so desperately needed from the one country that had secretly expressed sympathy for their faltering revolution—France. Soon after came the offer of the prize that Franklin had never requested: a military alliance and virtually unlimited access to the French treasury.

Taking Paris by storm:

**Benjamin Franklin,**
American Founding Father and first ambassador to France

by T. J. Fleming, USA

Thomas Fleming is an American historian from New York, NY. He received a Bachelor’s degree, with honors, from Fordham University in 1950, and became a full-time writer in 1960. His particular interest in the American Revolution is reflected in more than forty nonfiction books and novels, including acclaimed biographies on George Washington, Thomas Jefferson, and Benjamin Franklin. He contributes articles to such magazines as American Heritage, Military History, History Today, and MHQ, the Quarterly Journal of Military History. He has been involved in many societies, and served as president of the Society of American Historians and the PEN American Center, honorary member of the New York State Society of the Cincinnati, chairman of the New York American Revolution Round Table, and is a senior scholar at the Valley Forge American Revolution Center. (See http://thomasflemingwriter.com)

If you would not be forgotten, as soon as you are dead and rotten, either write things worth reading, or do things worth the writing.” True to his word, Benjamin Franklin did both, witness the more than 20,000 people who on his death in 1790 in Philadelphia came to pay their last respects to “the harmonious human multitude.” Polymath, as his affectionate moniker suggests, he was a pioneer in the study of electricity and inventor of the lightning rod, applied his insights to medicine, was a musician and deviser of the glass harmonica, experimenter, writer and publisher, diplomat, and a Founding Father of the United States of America, while also striving throughout life to cultivate thirteen virtues enumerated in his autobiography, wisely working on but one a week and “leaving all others to their ordinary chance.” These included Silence—“Speak not but what may benefit others or yourself; avoid trifling conversation” and Industry—“Lose no time; be always employ’d in something useful.” By Franklin’s own admission, oftentimes he fell short, but believed—who would doubt him?—that it made him a better man. And what a man! Self-taught and self-made. The man who by lauding devotion to education and hard work, egalitarianism, thrift, charity, and a spirit of community helped shape his fellow Americans and the nation they were building. The man who took France and Paris by storm as a scientist and an ambassador and who by dint of character as much as words spurred Louis XVI of France and his ministers to aid and abet that emerging nation in its wavering struggle for independence from Britain. The man who rescued the American Revolution. The man who came to be universally seen as the quintessential American.

Medicographia. 2014;36:112-122 (see French abstract on page 122)
Benjamin Franklin by David Martin, 1767 (oil on canvas on panel, 127.2×101.1 cm). Located in the White House in Washington DC. © Corbis.
In the fall of 1776, Philadelphia, the capital of the new republic of the United States of America, was plunged into gloom. On July the 13, rebellious colonies had declared themselves independent from Great Britain. Now their soldiers were being routed on all fronts. A once promising invasion of Canada had collapsed. Rumors of an imminent invasion of the Southern colonies multiplied. General George Washington and his Continental Army would soon be a dwindling remnant of the hopeful host that had challenged the main British army in the battle for control of New York City.

**George Washington's special envoy to France**

America needed help, massive amounts of help. To procure that assistance, they turned to the only man in Philadelphia who could obtain it—Benjamin Franklin.

This balding bullnecked seventy-year-old man was world famous. His discoveries in the science of electricity had astonished the globe from 1748 to 1749. In a daring experiment, he had demonstrated that lightning and electricity were one and the same. Everywhere in cities and towns, lightning rods now protected houses from destruction. Simultaneously, he had won fame as the publisher of *Poor Richard's Almanac*, an annual collection of witty aphorisms and predictions under the pen name Richard Saunders. He was also the editor of the most successful newspaper in America, the Pennsylvania Gazette. The British appointed him postmaster general for America, a job that enabled him to meet and fascinate prominent Americans in every colony.

For twenty years before the Revolution, Franklin had lived in London, hobnobbing with men of wealth and power, acting as spokesman for the colonies as their relationship with the Mother Country became more and more unhappy. In 1754, when war with the French colonies in America loomed, he had proposed a solution: a union of all the English colonies, to be supervised by a governor general. He backed the idea with the world’s first political cartoon: a snake chopped in several pieces above the words: **JOIN OR DIE...** Both Americans and Britons rejected this visionary idea, but it demonstrated Franklin’s ability to think in large and daring political ways.

This son of a Boston soap boiler had risen to hitherto unobtainable heights, thanks to his unique combination of intelligence and talent. When the tension with England exploded into violence in Massachusetts in 1775, he published an open letter to an English friend who was a member of Parliament.

> You have begun to burn our towns and murder our people. Look upon your hands. They are stained with the blood of your relations! You and I were long friends. You are now my enemy and I am yours – B. Franklin.

A full year and a half before the Declaration of Independence, Franklin demonstrated his ability to speak for the American people. It made perfect, if not painful, sense for the members of the Continental Congress to turn to Franklin to seek the help they so desperately needed from the one country who had secretly expressed sympathy for their faltering revolution—France.

The decision filled Franklin’s mind with gloom. It meant a winter voyage across the Atlantic. For a man his age, that ordeal might be a death sentence. The Atlantic also swarmed with British cruisers. If one of these men-of-war captured him, he would face a traitor’s death by public execution in London, but Franklin’s total commitment to the American cause was emphasized when he turned to the man sitting beside him in Congress, a young doctor named Benjamin Rush, and said, “I am old and good for nothing... my country may command my services in any way they choose.”

**Rough crossing**

Soon Franklin said what he probably thought was his last goodbye to his daughter Sally and his son-in-law, Richard Bache. Climbing into a coach with him were two of his grandsons. Seventeen-year-old William Temple Franklin was the son of Governor William Franklin of New Jersey, who had decided to remain loyal to the king, and was now in a prison in Connecticut. Also with him was Sally’s oldest son, seven-year-old Benjamin Franklin Bache. Franklin had decided to bring both boys with him to protect them from English influence should the British army capture Philadelphia.

Soon the three travelers were boarding *Reprisal*, the small American sloop of war. With her sixteen guns, they were about to challenge the wintry Atlantic, patrolled by a British fleet that mustered 1200 much larger cannons. Like Franklin, the Americans seemed to have little on which to rest their faith in their destiny beyond an inner conviction that a nation committed to freedom had a special mission in the world. In a letter Franklin

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**Political cartoon** of a snake cut into eight segments created by Benjamin Franklin for *The Pennsylvania Gazette* on 9 May 1754. It was used during the American Revolutionary War to encourage the thirteen American colonies (represented by their initials) to unite. © akg-images/Interphoto.
wrote the day before he sailed, Franklin put this faith into unforgettable words. "I hope our people will keep up their courage. I have no doubt of their finally succeeding by the blessing of God, nor do I have any doubt that so good a cause will fail of that blessing."

Four weeks later, on December 3, 1776, Breton sailors rowed Franklin and his grandsons ashore at the fishing village of Auray. He was so exhausted he could barely stand. The voyage had been a perpetual struggle against mountainous seas. The food had been abominable, nothing but salt beef and ship's biscuits. The cold had been agonizing; Franklin took to wearing a gray marten fur hat he had bought when he journeyed to Canada the preceding winter to offer diplomatic help to the American invasion.

The fishermen of Auray spoke a strange mixture of French and Gaelic and were utterly baffled by this stranger from the New World. No one in the little town had ever heard of Benjamin Franklin. The would-be ambassador hired a messenger to take a letter to Silas Deane, the Connecticut congressman sent to Paris earlier in the year to hire professional soldiers and buy munitions and weapons from the French government. "I am weak," he wrote. "But I hope the good air I breathe on land will reestablish me."

It took twenty-four hours for Franklin to obtain a wreck of a carriage and three decrepit horses to take him and his grandsons to the port of Nantes, where he would have landed but for contrary winds. The presence of the two young men may have suggested to some people that Franklin was combining diplomacy with the rescue of the remnants of his family from imminent capture. The British government was soon describing his voyage as a flight to escape a rebel's fate on the gallows.

**Nantes and Paris abuzz about “the most famous living American”**

Franklin’s reception in Nantes was stunningly different from the peasant puzzlement of Auray. His messenger to Deane had reported his arrival and Nantes was in an uproar. Franklin’s name was well known to the merchants and shippers of the prosperous port city. He was world famous for his discovery of electricity and the invention of the lightning rod. Twenty years later, his book of aphorisms and preachments on how to succeed in business, *The Way to Wealth*, written under the pen name Richard Saunders, had been published in France and read with enthusiasm by the rising bourgeoisie, who dubbed the author Bon Homme Richard. Ignoring Franklin’s murmured pleas that he needed rest; Nantes’s merchants staged a gigantic public dinner for him.
In Paris, a very different drama was taking place. The Comte de Vergennes, France’s cautious Foreign Minister, was in a swivet. Franklin’s arrival could not have been more inopportune. In several ports, no less than eight French ships were loaded with war materiel that Vergennes had decided to smuggle to America using a dummy company created by one of his secret agents, the playwright Caron de Beaumarchais.

Vergennes ordered the police chief of Paris to arrest anyone heard predicting that Franklin’s arrival was a signal that France would sign a treaty of alliance with the upstart American republic. This was the total opposite of what Vergennes would do, if the reports of American armies being routed on all fronts proved true. He was acutely aware that a war with England could bankrupt the French government.

Invisibility was opposite of the course Franklin intended to pursue. By this time, he had met Beaumarchais’s colleague, Jacques Donatien Leray de Chaumont, a tiny man who had made a huge fortune in the East Indian trade and purchased the fifteenth century Chateau of Chaumont. The diminutive merchant had already advanced Deane one million livres—about $250,000—out of his own pocket.

Chaumont undertook the job of publicizing Franklin to the French people. He had a ceramics factory on his estate and the services of a first-rate Italian artist, Giovanni-Batista Nini. Working from a sketch Franklin gave him, Nini created a portrait of Franklin wearing another fur hat, one made famous bourg, who had translated many of his writings, was so excited by his imminent appearance that he was a one-man publicity machine, all but shouting his praise of Franklin and the American Revolution in all directions.

Voltaire, the guiding spirit of the French enlightenment, wrote to a friend lamenting that “Dr. Franklin’s troops” had been defeated in battle after battle. Franklin had no interest in the sage’s military opinions. It was Voltaire’s description of a Pennsylvania he had never visited, an idyllic place peopled by simple honest Quakers that Franklin was planning to put to good use. He arrived at the Hôtel de Hambourg wearing the marten fur hat that had preserved him on the freezing Atlantic.

Paris buzzed with excitement. No distinguished person in memory had dared to appear in public without a wig. They also noted with amazement that Franklin was in the “complete costume” of the Quaker sect, with “extremely white linen” and a plain brown suit. It was only a step to another observer concluding: “Everything about him announces the simplicity and innocence of primitive morals.”

Those latter words resonated enormously with the French. Along with Voltaire’s description of Pennsylvania’s social democracy, everyone had read philosopher Jean Jacques Rousseau’s call for a return to the unspoiled morals of the noble savage. A recapture of this totally imaginative primitive state was France’s only hope of escaping the rituals, finery, and corruptions of its civilization.

France faces difficult choices

Meanwhile, in the Hôtel de Hambourg, Franklin rapidly acquired a grasp of Silas Deane’s plans to smuggle weaponry to America with Beaumarchais’s help. Neither man knew that the Comte de Vergennes had already issued an edict, forbidding a single ship to sail. The foreign minister soon met with Deane, Franklin, and a third diplomat, the Virginian born Arthur Lee, who had been appointed when Thomas Jefferson declined to serve because of his wife’s fragile health. Vergennes stressed that the Americans should make themselves as invisible as possible, lest they arouse England’s wrath.

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by Rousseau. Soon Chaumont was turning out thousands of terra cotta medallions, which he sold throughout France. None too subtly underscoring their partnership, Franklin soon accepted an offer to live on Chaumont’s estate, which was in the suburb of Passy, on the road to Versailles and Vergennes’s offices. In further conferences with Vergennes, Franklin never said a word about a military alliance, which the Americans desperately needed. All he offered was a commercial treaty that would give France access to America’s trade, but in every meeting Franklin’s remarkable personality worked its magic on the veteran diplomat. In a matter of weeks, Vergennes offered another two million francs in secret aid from the French treasury.

The ladies’ man
Two weeks after Franklin’s arrival, he accepted an invitation from the eighty-year-old Marquise du Deffand whose twice-weekly salon was the foremost social destination in Paris. Once more he wore his fur hat and Quaker costume. The Marquise was blind and hence immune to the shock, but the rest of the bewigged silk-clad aristocrats in the packed room were speechless with amazement.

It was by no means the last salon Franklin visited. From previous visits to France, he knew that French women played an extremely important role in forming public opinion and even in influencing political decisions. Franklin found himself delighted by the feminine wit and intelligence that soon surrounded him. Writing to his sister Jane, he said he found the company of French women “extreamly [sic] agreeable.”

France being France, the ladies had no hesitation about kissing Franklin and inviting him to reciprocate, which he did with enthusiasm. “Somebody,” he told a Boston niece, “gave out that I loved ladies; and then everybody presented me their ladies (or the ladies presented themselves) to be embrac’d – that is to have their necks kiss’d...The French ladies have a 1000 other ways to render themselvesagreeable, by their various attentions and civilities, & their sensible conversations.”

Franklin became a master of dealing with large groups of women. When one of them came close enough to ask whether he liked her more than her nearby competitors, the discoverer of electricity would assure her that she was his choice, as long as she was close to him, “because of the power of the attraction.” Needless to say, the lady was thrilled.

What makes Franklin’s popularity with the ladies doubly amazing was his limited command of the French language. “If you Frenchmen would only talk no more than four at a time, I might understand you and not come out of an interesting party without knowing what you are talking about,” he remarked to a French friend. In large groups, Franklin made it a policy to remain silent—which the voluble French promptly turned into another Franklin virtue.

John Adams, the grumpy puritan
By the time John Adams arrived in early 1778 to replace Silas Deane, there was only one American name on everyone’s lips: Franklin. “His name was familiar to government and people,” the envious Adams groused. “To foreign courtiers, nobility, clergy and philosophers, as well as plebeians, to such

A TOUCH OF FRANCE
Benjamin Franklin takes Paris by storm – Fleming

Portrait of Benjamin Franklin sporting his signature marten fur hat. Painting by John Trumbull (1756-1843), Located at Yale University Art Gallery (Peabody Archaeology, Art, and Ethnology Museum. © akg/De Agostini Picture Library.

Benjamin Franklin and the Ladies
(from a letter to Mrs Partridge, October 11, 1779)
You mention the Kindness of the French Ladies to me. I must explain that matter. This is the civilest Nation upon Earth. Your first Acquaintances endeavour to find out what you like, and they tell others. If ‘tis understood that you like Mutton, dine where you will find Mutton. Somebody it seems, gave it out that I lov’d Ladies; and then every body presented me their Ladies (or the Ladies presented themselves) to be embrac’d; that is to have their Necks kiss’d. For as to kissing of Lips or Cheeks, it is not the Mode, here, the first, is reckoned rude, & the other may rub off the Paint. The French Ladies have however 1000 other ways of rendering themselves agreeable; by their various Attentions and Civilities, & their sensible Conversation. ‘Tis a delightful People to live with.
a degree there was scarcely a peasant or a citizen, a valet de chamber, coachman or footman, a lady’s chamber maid or scullion in a kitchen who did not consider him a friend….When they spoke of him, they seemed to think he was to restore the Golden Age. His plans and his example would abolish monarchy, aristocracy and hierarchy throughout the world.”

Similarly, the humorless Adams called Franklin’s daily routine “a scene of continual dissipation.” He usually partied until midnight and seldom arose early enough to discuss the business of the embassy with Adams before breakfast. No sooner was that meal consumed, than “a crowd of carriages” brought a small army of visitors. Adams dourly chronicled them as “philosophers, academicians and economists…but by far the greater part were women and children come to have the honor to see the great Franklin and to have the pleasure of telling stories about his simplicity, his balding head and scattering straight hairs.” Media-minded contemporary Americans can only shake their heads at Adams’ failure to understand that all this was part of Franklin’s stunningly successful publicity campaign.

A French physician friend, Pierre George Cabinis, expressed the delight so many of his countrymen and women felt for Franklin. His “most original trait,” Cabinis said, was his “art of living” which enabled him to combine business with pleasure without the slightest hint of a conflict. “No matter when one asked for him, he was always available. His house in Passy…was always open for all visitors. He always had a half hour for you.”

**Franklin, Mozart, and the glass armonica**

Another less well-known side of Franklin’s charm offensive was music. Again, the disgruntled Adams fills us in on this amusement in his morose way. He tells us that after a dinner party thronged with VIPs, which usually began about three and ended about six, Franklin would “most commonly” visit women friends. They served him tea in the English fashion. “After tea the evening was spent in hearing the ladies sing and play upon their piano fortés and other instruments of musick.” Many of these women were gifted performers. Franklin’s Passy neighbor and closest woman friend, Madame Brillion de Jouy, was a pianist well enough known to have several of Europe’s leading musicians dedicate compositions to her.

Franklin’s favorite melodies were the traditional songs of Scotland and Ireland. He could also join in musicales on the violin, the harp, or the guitar. Even more important was an instrument he had invented—the armonica, which he had perfected in 1762. It consisted of several glasses of different sizes, in the shape of hemispheres, with an iron spindle passing through holes in the middle of each glass. A player worked the spindle with a treadle while touching the edges of the moving glasses with his fingers. Even before Franklin arrived...
in France, the armonica’s eerie otherworldly music was very popular. Queen Marie Antoinette learned to play it as a girl in Vienna, and both Mozart and Beethoven composed music for it. Imagine the rapture with which the ladies of Paris listened to the inventor of the instrument playing it in their sitting rooms.

Franklin’s witticisms set Paris roaring with laughter
Franklin found time to indulge in a pastime he had perfected in his days as a newspaper editor: skewering his enemies with deadly wit. Franklin and the French foreign minister Vergennes knew they were surrounded by spies on the payroll of the British ambassador, Lord Stormont, who assiduously fed the newspapers vicious slanders of Franklin and reports of the collapse of George Washington’s army. When a distressed French friend asked Franklin if one of these stories was true, he gravely replied, “Oh no, it is not the truth. It is only a Stormont.” The bon mot swept through Paris and Stormont became a new synonym for lying.

Around the same time, Franklin dealt with another member of the British establishment, Edward Gibbon, who had been publishing to great acclaim his monumental *Decline and Fall of the Roman Empire*. Franklin had met the historian during the years he had spent in London trying to prevent the Revolution from erupting. One night, dining at a popular eatery, Franklin saw Gibbon at a nearby table and sent him a note, suggesting they have a drink together. Gibbon pompously replied that a loyal servant of George III could not talk to a rebel. Franklin scribbled his regrets and added that if Mr Gibbon ever wrote a book on the decline and fall of the British Empire, he was ready to supply him with “ample materials.” It was another witticism that became a staple in Paris’ cafes.

When he learned that Washington had captured almost a thousand Hessians in a surprise attack at Trenton, he wrote an essay, supposedly from the Count de Shaumbergh of Hesse-Cassel to Baron Hohendorf, the commander of the Hessian troops in America. “You cannot imagine my joy at being told that of the 1950 Hessians engaged in the fight, but 345 escaped. There were 1605 men killed and I cannot sufficiently commend your prudence in sending an exact list of the dead to my minister in London.” The Count was getting paid per

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**Glass armonica** (no “h” as armonica is derived from the Italian language) attributed to Benjamin Franklin, bequeathed to the Bakken Museum by the descendants of Madame Brillon, a friend of Franklin. © Collections of The Bakken Museum, Minneapolis MN, USA.

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**Backside view of the Café Procope**, on Cours du Commerce Saint-André, Paris 6th. In the windows, the medallion on the right features Benjamin Franklin, a frequent patron; the medallion on the left portrays French Revolutionary Robespierre (1758-1794). Café Procope is the oldest Paris restaurant in continuous operation, opened in 1686 by a Sicilian, Francesco Procopio dei Coltelli. It soon became a meeting place for intellectuals and revolutionaries. Photo courtesy of Frederick Scheffler.
casualty and he looked forward to collecting 643,500 florins from the British exchequer. “I’m about to send you new recruits,” crowed the Count. “Don’t economize them.” The Count’s recent trip to Italy had cost him “enormously” and he had contracted for a “grand Italian opera” which threatened to empty his treasury. He urged the Baron to “encourage as much mortality as possible” by exhorting the newcomers to “seek glory in the midst of dangers.” The essay was read aloud in cafes and salons of Paris, to roars of delighted laughter.

Franklin takes on the British fleet
Then, there was Franklin’s role as self-appointed admiral, which never made the newspapers, but was also the talk of a British-hating Paris. Using French funds, he ordered the commander of the USS Repziel, Captain Lambert Wickes, to carry the war into England’s home waters. With a squadron of three ships, Wickes captured eight vessels and destroyed ten others off the Irish coast. Next, Admiral Franklin unleashed another fighting sailor, Gustavus Coyningham, who sailed completely around the British Isles, destroying numerous ships in the North Sea and the Baltic. Insurance rates in London soared and British merchants began using French ships. Franklin was soon telling people there were forty French merchantmen in the Thames, taking on cargo. It was another story that won chortles and applause from Paris to Nantes.

France wavers… and rallies: c’est la guerre!
Meanwhile, the war in America rumbled on, and except for Washington’s small victories at Trenton and Princeton, the news remained bad. The most crushing report, rushed from London by George III’s elated secret agents, was the capture of the American capital—Franklin’s home city of Philadelphia—by the British army’s commander in chief, Sir William Howe. Franklin’s daughter, son-in-law, their younger children, and all the property Franklin owned were now in the enemy’s hands. Publicity, Franklin remained undaunted. A few days later, a guest at a dinner party asked him about it with obvious malice in his voice. “Well Doctor, Howe has taken Philadelphia.” “I beg your pardon, sir,” Franklin shot back. “Philadelphia has taken Howe.”

There was truth as well as wit in his answer. Franklin was a chess player and he saw with a glance at a map that the city was only a symbolic conquest. The British army was in a sea of hostile Americans and dependent on the winding Delaware...
River for supplies, but diplomats deal in symbols as well as realities. Franklin and his fellow diplomats were more than a little disheartened. A week later, a rumor came drifting into Paris from Nantes. An American ship had arrived with a messenger carrying important dispatches for the American envoys. The three diplomats and many of their French friends gathered at Franklin’s Passy house on the day this courier was likely to arrive. When a chaise rattled into the cobblestone courtyard, they rushed out to greet it.

Thirty-year-old Jonathan Loring Austin of Boston climbed out and introduced himself. “Sir,” Franklin asked, “Is Philadelphia taken?” He and everyone else had been hoping the story was another “Stormont,” but Austin only nodded mournfully. “Yes,” he said.

Franklin’s head drooped. With a sigh, he turned away, deeply dismayed. He had taken about two steps when Austin said: “But sir, I have greater news than that. General Burgoyne and his whole army are prisoners of war!”

Beaumarchais leaped into his carriage and thundered into Paris to spread the news. At Passy, Franklin concentrated on getting it to Versailles and Foreign Minister Vergennes. For a little while, there was some diplomatic hesitation in Versailles. This vanished when Franklin allowed French spies to learn he was talking to the head of the British secret service in France about the possibility of signing a peace of reconciliation with the Mother Country.

It meant war with England, but for Parisians it also meant a partnership with the man they had come to admire and love more than any other foreigner in the civilized world, Bon Homme Richard, the sorcerer who had tamed the lightning from heaven, and would now help them defeat their oldest and most arrogant enemy.

**Quaker meets king**

The climax of the drama came on March 20, 1778, when Franklin, with the treaty signed, journeyed to Versailles for an audience with Louis XVI. It was also the ultimate performance of Bon Homme Richard, the imaginary Quaker. Franklin wore neither wig nor sword nor any other decoration on his simple brown suit and spotless white stockings and shirt. It is hard
for us to grasp how daring this costume was at Versailles. Dress in the palace was as carefully regulated as the ritual of a solemn high mass at St. Peter’s Basilica in Rome. The royal chamberlain frequently barred those who violated the rules.

In the palace courtyard, when Franklin debarked from his carriage, a gasp ran through the huge crowd of spectators. “He is dressed like a Quaker,” ran the half-frightened whisper. From Vergennes’s apartment in a wing of the palace, Franklin and his fellow envoys were led down seemingly endless corridors to the door of the royal apartments. Noblemen lined the walls, murmuring their amazement at Franklin’s daring.

At the door, the royal chamberlain almost went into shock at the sight of Franklin’s outfit, but he controlled himself and led the visitors to the King’s dressing room. Louis met them with a lack of ceremony that suggests Vergennes had prepared him for the visit. He wore a loose robe and his hair hung down to his shoulders. “Firmly assure Congress of my friendship,” the young king said. “I hope this will be for the good of the two nations.” He added that he was “exceedingly satisfied with your conduct during your residence in my kingdom.”

Franklin replied, “Your Majesty may count on the gratitude of Congress and its faithful observance of the pledge it now takes.” The Americans trudged back down the immense corridors to the courtyard, where the crowd was still immense. The sight of Franklin triggered a total abandonment of palace etiquette. They burst into a tremendous cheer. There is a tradition that Franklin was so moved by it, he wept. The affection of these spontaneous people was a unique tribute to his ability to win hearts as well as change minds in the service of his country.
Franklin recognized risks with alcohol: ‘Take counsel in wine, but resolve afterwards in water’; but also rewards: ‘There’s more old Drunkards than old Doctors.’ His wine collection in France included 1203 bottles in 1782. He facetiously wrote that the arm was designed to allow man to consume wine. Using his grandson’s illustrations, he demonstrated that if the elbow were closer to either the hand or the shoulder, raising a glass of wine to the mouth would be impossible.

Benjamin Franklin took the title of “Doctor” after receiving an honorary Doctor of Laws degree in 1759 for his contributions in understanding electricity. Although not formally trained in medicine, he could have also claimed this title as a physician, as he often provided medical advice, helped found a hospital, performed medical experiments, invented medical devices, promoted smallpox inoculation, studied the effects of lead poisoning, and supported medical education. Because of Franklin’s scientific and analytic powers, Louis XVI chose him to join a nine-member commission to investigate the claims of Franz Mesmer about “animal magnetism” and his ability to cure numerous disorders. He recognized the “placebo effect” in patients’ responses to treatment. He made astute observations about his own illnesses, including the first good description of psoriasis. He suffered from gout and bladder stones, but faced his infirmities with equanimity and good humor. These achievements display his capacity for detailed, perceptive insights, his fastidiousness in recording his observations, his thoughtful analyses of scientific phenomena and human conduct, and his graciousness in adversity. In many ways, he was an exemplary doctor.
After publishing his *Experiments and Observations on Electricity* in 1751, Benjamin Franklin (1706-1790) became a famous scientist. He coined much of the vocabulary of electricity, including the names for charges (positive or plus and negative or minus), and the words battery, condenser, discharge, electrician, and conductor, among others. He recognized the importance of grounding, and formulated the law of conservation of charges. With his famous experiment of flying a kite during a thunderstorm, he demonstrated that lightning was an electric phenomenon, therefore establishing electricity—previously considered an interesting, but inconsequential oddity—as an important force in nature. Always concerned to find a practical application for scientific discoveries, he invented the lightning rod, which preserved buildings from the devastating fires that so often followed lightning strikes. Paraphrasing the claim that Emperor Augustus “found Rome brick and left it marble,” one biographer, Carl Van Doren, stated that Franklin “found electricity a curiosity and left it a science.”

To recognize these contributions, the University of Saint Andrews in Scotland bestowed upon him an honorary Doctor of Laws degree in 1759—even though his formal schooling had ended at age 10—and, thereafter, he was called “Doctor Franklin.” Despite his lack of training, he could also have claimed that title in the medical sense, for he provided advice about health, treated patients, shrewdly observed his own illnesses, and made numerous contributions to medicine, both scientific and civic.

**Advice about health**

- **Advice on diet**
  Franklin advocated moderation in eating, especially in *Poor Richard’s Almanack*, a paperback compendium of diverse information—such as tide charts, weather forecasts, recipes, adages, and astronomic observations—that he published annually from 1733 to 1758 under the pseudonym of Richard Saunders. It contained several dietary aphorisms: “Eat to live, and not live to eat”; “To lengthen thy Life, lessen thy Meals”; “A full Belly makes a dull Brain.” Despite claiming a “perfect inattention” to food, however, Franklin loved eating, and his papers contain numerous recipes. No portraits depict him during youth, but when 49, he described himself as “a fat old Fellow,” and pictures thereafter confirm his corpulence. His recommendations and habits therefore diverged, or, as he stated, “Saying and Doing have Quarrel’d and Parted.” He acknowledged this inherent human failure, when he said of advice, “there is, perhaps, no other valuable Thing in the World, of which so great a Quantity is given, and so little taken.”

- **Alcohol**
  Franklin recognized both risks and rewards with alcohol. He recommended caution: “Take counsel in wine, but resolve afterwards in water”; “He that drinks fast, pays slow.” He also asserted, however, “There’s more old Drunkards than old Doctors,” and his wine collection in France included 1203 bottles in 1782. Moreover, he facetiously wrote that the arm was designed to allow man to consume wine. Using his grandson’s illustrations, he demonstrated that if the elbow were closer to either the hand or the shoulder, raising a glass of wine to the mouth would be impossible (see page 130).

- **Exercise**
  Franklin stated that, to remain healthy, students should exercise. From his youth, he enjoyed swimming, and to increase his speed, he even devised hand paddles and sandals to function as fins. In London at...
A  TOUCH  OF  FRANCE

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Dr Benjamin Franklin’s scientific and medical legacy – Hirschmann

age 19, he displayed his aquatic prowess by swimming several miles in the Thames, performing many stunts along the way, and when nearly 80, swam across the Seine.

◆ Fresh air, Franklin’s theory of colds, and contagion
Franklin strongly endorsed fresh air, especially during sleep. He believed that people putrefy by shedding particles in their breath and sweat. Reinhaling them accelerates putrefaction and causes bad dreams. To diminish these dreams, Franklin recommended moderate eating, which provokes less sweat than a heavy diet, and wearing thin bedclothes to allow moisture to escape. If such dreams occurred anyway, he suggested airing the bedding and walking around undressed to allow the skin “to discharge its load.”

He also enjoyed cold morning air, and early each day he sat in his chamber nude for “half an hour or an hour, according to the season.” Its benefits were admittedly uncertain, but “at least it does not injure my health, if it does not in fact contribute much to its preservation.”

Franklin’s enthusiasm for fresh air caused a confrontation with John Adams, when they lodged in a tiny room. Fearing the evening air, Adams, who was suffering from a cold, shut the window. Franklin instructed him to open it. Adams recalled,

The Doctor then began an harangue, upon Air and Cold and Respiration and Perspiration, with which I was so amused that I soon fell asleep, and left him and his Philosophy together. Franklin did not catch Adams’ cold.

The theory that Adams found soporific differed from the prevailing view that colds arose from dampness or low temperatures. Franklin argued against that theory by citing his own experience of numerous exposures to cold and dampness that failed to cause a cold and by pointing out that people at sea or those who live in climates where the air is constantly moist do not seem more predisposed to colds than those living in areas with drier air. Instead, he felt that colds occur from inhaling others’ perspirations or exhalations, either directly or through contaminated materials, such as clothes and bedding. He also blamed “too full Living” and inadequate exercise. He wondered, however, whether “some unknown Quality in the Air…produce[s] Colds, as in the Influenza.” In recognizing their contagiousness and dissemination through inhaling material exhaled by others, Franklin came close to the idea that colds develop from infectious particles. He had a similar sense of contagion when he pondered the duration that dead bodies remain infectious. He recounted a newspaper article describing a woman’s burial beside her husband, who had died of smallpox 30 years earlier. The gravedigger inadvertently

![The Historic Pennsylvania Hospital](image)

The Historic Pennsylvania Hospital] founded thanks to the money raised by Benjamin Franklin (statue is in the foreground). © Bob Krist/Corbis.
broke into the old coffin, causing a foul smell to emanate. Days later, 25 of the mourners developed smallpox, a disease that had been absent from that village for 30 years. He also mentioned that several physicians in London died of a “malignant fever” after attending a dissection of an Egyptian mummy and that two members of the Royal Society became ill the day after examining the dried body of an ancient inhabitant of the island of Tenerife.

Contributions to medicine
◆ Founding of Pennsylvania Hospital and the encouragement of medical education
In 1751, Dr Thomas Bond (1713-1784) sought Franklin’s assistance in starting a hospital in Philadelphia for sick indigents and the mentally ill. Franklin applied for money from a reluctant Pennsylvania Assembly, asking them to match funds if he could raise £2000 from the public, an amount that the Assembly thought unattainable. Certain that Franklin would fail, the representatives agreed, wanting to appear sympathetic without incurring any expenditure. In his appeal to the public, Franklin noted that the prospect of the Assembly’s matching funds meant that “every Man’s Donation would be doubled,” and that hospital care was at least 10-fold cheaper than treatment in private lodgings. Franklin’s scheme succeeded, and Pennsylvania Hospital opened in 1752. His further contributions to Pennsylvania Hospital included serving as its manager, secretary, and president; helping write its bylaws; designing its seal; and writing the cornerstone’s inscription. Franklin wanted it to be a teaching hospital, where exposure to diverse patients would increase the experience of established physicians and would provide students with the skills to establish practices in other locations. Franklin also encouraged medical education through writing letters of recommendation for promising students in Philadelphia to study medicine in Edinburgh and London.

◆ Electric therapy and the “placebo effect”
In 1750, Franklin used Leyden jars, foil-coated glass bottles that stored static electricity, to electrocute a turkey, which he later roasted for Christmas. In the process, he accidentally shocked himself. This experience and claims of medical benefits of electricity may have encouraged Franklin to treat paralyzed patients with thrice-daily shocks to their palsied limbs. Some strengthened, but the therapy was painful, the benefits brief. Franklin was unclear how to explain any improvement: whether from the Exercise in…coming daily to my House, or from the Spirits given by the Hope of Success, enabling them to exert more strength in moving their Limbs.

Franklin was proposing a “placebo effect” 200 years before it became an accepted phenomenon in medicine.

Franklin had one apparent triumph, a young woman with numerous “hysteric symptoms.” After many twice-daily shocks, her health improved. Perhaps Franklin had performed electroconvulsive treatment. He did advocate electrical therapy for the insane, after hearing from a physician who, mentally reenergized following a shock, suggested that it might be therapeutic for such patients.

◆ Flexible urethral catheter
Previous catheters, made of metal, wood, or stiffened animal skins, were rigid enough to navigate the male urethra without buckling, but had difficulty traversing the curves, causing great pain. For his brother, who had a bladder stone, Franklin designed a flexible metal catheter, comprising several hinged...
silver segments. He enclosed a wire inside the catheter to increase its rigidity during insertion, and recommended smoothing its surface with animal gut or tallow. Like a screw, it was "both withdrawn and introduc’d by turning."

**Lead poisoning**

Although others had described lead poisoning earlier, Franklin recorded perceptive observations in 1786. He remembered that people in North Carolina complained that New England rum impaired the use of their limbs and caused "dry belly-ache," episodes of abdominal pain and constipation now called "lead colic." After doctors implicated lead in the distilling equipment, the Massachusetts legislature prohibited its use in 1723. In 1724, Franklin saw printers drying a case of lead types, employed for printing, in front of a fire. An old workman warned that this practice could cause problems with the hands, an effect that Franklin observed in a coworker, who had the "dangles"—wrist drop from radial neuropathy. He noticed that a whole family developed "dry bellyache" after drinking rainwater collected from a leaded roof. To confirm the cause of this condition, Franklin studied patients treated for it in a Paris hospital and found that, as expected, all had prior lead exposure.

**Smallpox inoculation**

Smallpox (variola) appeared in the American colonies in the 17th century, spread rapidly, and conferred a mortality rate of 15% to 30%. It was long known that one attack prevented future ones, for smallpox never recurred in a pockmarked person. It was also recognized that "varilication"—inoculating a victim’s pus into the skin or nose of someone previously uninfected—caused a milder attack than naturally-acquired disease. Although smallpox following inoculation was sometimes lethal, variolation was beneficial: in the 1721 Boston epidemic, for example, 2% of those inoculated died, compared with 15% with natural disease. Unfortunately, inoculated individuals could still transmit smallpox to others, with the expected mortality rate of the naturally-acquired infection.

Franklin promoted variolation in the 1750 *Poor Richard’s Almanack* and tackled the objection that deliberately infecting a person with smallpox was immoral because it interfered with God’s will. Instead, he argued that it was "impious to reject a Method discovered to Mankind by God’s good Providence, whereby 99 in 100 are saved," compared with the "natural" mortality of one in seven.

Franklin recruited the distinguished British physician, William Heberden (1710-1801)—who famously provided the first clinical description of angina pectoris—to write a pamphlet describing smallpox inoculation and its consequences. In his introduction, Franklin delineated the advantages of variolation during the 1753 Boston epidemic and provided information from a London smallpox hospital: a 0.4% mortality for variolation compared with 26% in the uninoculated. He dispatched 1500 free pamphlets to Philadelphia to persuade poor parents to variolate their children and in 1774 raised money for free inoculation of the indigent. Variolation remained the major method of containing smallpox until 1798, when Edward Jenner (1749-1823) promoted inoculation with cowpox (vaccinia) as a safer procedure.

**Franklin and bifocals**

Franklin was farsighted ("hyperopic" or "hypermetropic"), and with age required spectacles to see objects in the middle distance. He also developed presbyopia—trouble seeing fine print and near items—which was correctable with another set of lenses. Franklin alternated between two different spectacles when viewing close or more distant objects. Finding this process unwieldy, he had a single pair of lenses cut horizon-
a fine fluid was present throughout creation, and sickness developed from something obstructing the flow of this “animal magnetism.” Certain individuals, especially himself, could eliminate the blockage by pointing a finger or rod toward the patient’s head, intensely gazing into the eyes (“mesmerizing”), pressing on the abdomen, or rubbing various areas. Mesmer invented the baquet, a covered tub holding bottles of “magnetized” water attached to metal rods that patients pressed onto ailing body parts. When exposed to magnetism, patients often experienced “crises,” which included such reactions as hiccoughs, convulsions, fainting, and uncontrollable laughter.

To examine the purported action of magnetized water, the commissioners sat around a baquet numerous times, with...
out any discernible effect. Franklin and several acquaintances, when “magnetized,” felt no significant change. In Franklin’s orchard in Passy, an apricot tree was magnetized, which, according to Mesmer, should produce crises in susceptible people as they neared it. A 12-year-old boy, previously reactive to treatments, was blindfolded and successively taken to distant, nonmagnetized trees, where he had a crisis. When the commissioners blindfolded another susceptible patient and pretended to magnetize her, she had a crisis. In a subsequent test, they had one container of water magnetized, but gave nonmagnetized ones to her. Again, she had a crisis. After asking for a drink, she unknowingly consumed the magnetized water without having any reaction and had none when the commissioners surreptitiously placed a magnetized container behind her.

Based on these and other experiments, the commissioners determined that the observed responses were unrelated to animal magnetism, but arose from imagination, aided by hope. People suffering from some problem wanted to get better and expected that a procedure authoritatively administered would help. Animal magnetism, however, was only a falsehood. The commissioners’ investigation was a remarkable scientific inquiry. They carefully examined Mesmer’s methods, scrupulously recorded their observations, and employed sham procedures and placebos to separate the effects attributable to the subjects’ suggestibility from those that might be due to animal magnetism, if it existed. Despite the report’s forceful discrediting of Mesmer’s claims, Franklin correctly anticipated that the concept of animal magnetism would not vanish quickly, for “there is a wonderful deal of Credulity in the World, and Deceptions as absurd have supported themselves for Ages.”

Other observations of medical interest

**Effect of color on heat absorption**

To investigate the effect of color on heat absorption, Franklin placed pieces of cloth of identical size, but different colors, on snow on a sunny morning and, returning later, noted that the darker ones created deeper indentations than the lighter ones, by melting more of the snow beneath them. Franklin considered the practical application of this observation that darker colors absorb more heat: on hot days people should wear white, rather than dark, clothing, especially with vigorous activity, which further increases body temperature and can cause lethal heat stroke.

**Evaporative cooling**

Franklin noticed that repeatedly wetting a thermometer with alcohol reduced the recorded temperature. He then used ether on the thermometer, and its rapid evaporation caused the mercury to drop several degrees. When he increased the rate of the evaporation of ether by blowing on the thermometer with a bellows, a thin coat of ice appeared on its tip. Again concerned about the practical implications of his observations, Franklin proposed that fanning oneself when warm really does cool the skin through increasing sweat evaporation, and that people could work in hot weather safely if they kept themselves hydrated enough to maintain abundant perspiration. He also suggested a medical application: when moisturizing dressings on an inflamed area, use alcohol rather than water, because it evaporates more rapidly, producing greater cooling and relief of the discomfort.

**Blood circulation**

Franklin was intrigued by the circulation of blood through the body and had a machine that reproduced it by having a red fluid pass from a reservoir into numerous capillary tubes of glass, then return to the reservoir. His interest in the mechanism of blood flow led him to wonder whether, in addition to contractions ejecting blood from the heart, “the ventricles … like Syringes, draw” blood into it. This proposal, that relaxation of the heart muscle after contraction sucks blood into the cardiac chambers, appears valid.

**His own illnesses**

**A chronic skin disease**

About 1774, Franklin noticed that scales appeared on his scalp and then on his extremities and lower back. His detailed accounts in 1777 indicate that he had psoriasis, which was not described in the medical literature until 1808 by Robert Willan (1757-1812). Franklin noted that the scale had several layers, like mica. Removing it produced bleeding, a characteristic finding of psoriasis now called Auspitz’s sign, named after Heinrich Auspitz (1835-1886), who described it about a century later. Franklin noticed other features of psoriasis: le-
sions improved in the summer, worsened during the winter, and appeared in areas of previous boils, a feature labeled the Koebner phenomenon because Heinrich Koebner (1838-1904) reported 100 years later that psoriatic patches formed at sites of recent skin damage, such as abrasions and skin infections. Franklin’s psoriasis eventually affected almost his entire body, sparing only his hands and face. After 14 years, his skin condition permanently subsided, following a severe attack of polyarticular gout.

◆ Gout

The disorder that apparently rescued him from his skin disease began in February 1750, at the age of 44. He was free from gout for 5 years between 1765 and 1770, but thereafter attacks became more numerous, often protracted, and sometimes severely disabling. They interfered with many of his duties while in London from 1770-1775 as an agent for several of the colonies, and often incapacitated him during his diplomatic tenure in France from 1776-1785. He had a severe attack just before signing the Declaration of Independence, and an extended bout in August and September 1782 delayed resolution of the Paris peace talks that ended the Revolutionary War.

Franklin recognized some of the predisposing factors for gout in his adage in 1734, “Be temperate in wine, in eating, girls & sloth; Or the Gout will seize you and plague you both.” He recognized some of those features in himself in “Dialogue between the Gout and Mr. Franklin,” a bagatelle written in 1780 after a particularly brutal episode. In it, he wonders why he should cruelly suffer from this disease. The Gout, personified, explains that Franklin brought it on himself through indolence, inactivity, gluttony, and excessive alcohol, but also mentions the longstanding, but erroneous, belief that gout protected its victim from other diseases.

Even in 1783 after several severe attacks, Franklin stated, “I have been lately ill with a Fit of the Gout, if that may indeed be called a Disease. I rather suspect it to be a Remedy, since I always find my Health and Vigour of Mind improv’d after the Fit is over.

Perhaps this attitude was the best approach to what was then an untreatable disease.

Another conviction about gout, dating from as far back as the Hippocratic writings, was that sexual excess precipitated attacks. Franklin was skeptical. In 1780, he responded to some verses about gout written by his friend Madame Brillon suggesting that “mistresses have had a share in producing this painful malady.” He playfully explained why he disagreed:

When I was a young man and enjoyed more of the favours of the sex than I do at present, I had no gout. Hence, if the ladies of Passy had shown more of that Christian charity that I have so often recommended to you in vain, I should not be suffering from the gout right now. This seems to me good logic.
Franklin had passed small stones for several years, but in 1782 he began to void ones the size of small peas. This problem resolved, but he continued to pass smaller bits, resembling sand. A year later, he noticed bloody urine and sometimes the abrupt cessation of flow in midstream, indicating bladder outlet obstruction. He found that lying on his side allowed him to resume urination. He also had pain when he suddenly turned or moved his body, walked on pavement, or traveled in a carriage. He ate honey, believing that it would increase the thickness of his urine and allow the gravel to float on top of it.

Franklin’s problem worsened, but he accepted his fate with equanimity: “People who live long, who will drink of the Cup of Life to the very Bottom, must expect to meet with some of the usual Dregs; and when I reflect on the Number of terrible Maladies human Nature is subject to, I think myself favour’d in having to my share only the Stone and Gout.”

He did have one option for relief—surgery. In Franklin’s time, the standard operation was perineal lithotomy. The surgeon inserted a metal rod through the urethra into the bladder to help localize and stabilize the stone. He made an incision near the anus, cutting through the prostate into the bladder, into which he passed a forceps to remove the stone. Because no effective anesthetics were available, three or four burly assistants tightly held the patient, who was also partially tied down, to prevent any movement during the excruciating procedure. Expert surgeons could complete the ordeal in a few minutes or less, but patients still faced the potential complications of fatal hemorrhage or infection. Those who survived often had lengthy convalescences, with slow healing and chronically draining wounds. Many had permanent urinary incontinence and impotence.

Franklin declined the operation. His decision was probably wise, for the procedure would likely have been fatal in someone his age, and the London doctors whom he had consulted advised against it. Unfortunately, his symptoms slowly worsened. In 1784, he likened himself to a building that required “so many Repairs that in a little time the Owner will find it cheaper to pull it down and build a new one.” The following year he wrote, “I have been these 20 Months past afflicted with the Stone, which is always giving me more or less Uneasiness, unless when I am laid in Bed.” Because the stone caused so much pain while riding in carriages, when he left France to return to Philadelphia in 1785, he traveled overland to the sea in a litter, a vehicle containing a couch surrounded by curtains, provided by Queen Marie Antoinette and borne by two Spanish mules.

In the summer of 1787, when he first took his seat at the Constitutional Convention in Philadelphia, he entered the chamber in an enclosed sedan chair carried by four men and resting on flexible rods to minimize painful jarring. In November 1787, he gamely suggested that temperance in eating, avoiding alcohol, and exercising the upper portion of his body with dumbbells would at least prevent the stone from enlarging. In 1789, he stated, “I have a long time been afflicted with almost constant and grievous Pain, to combat which I have been obliged to have recourse to Opium, which indeed has afforded me some Ease...
from time to time, but then it has taken away my Appetite and so impeded my Digestion that I am become totally emaciated, and little remains of me but a Skeleton covered with a Skin.

He faced his chronic illness and impending death with the same qualities that were so prominent in other phases of his life, whether dealing with success or frustration—good humor and equanimity. He died on April 17, 1790, asphyxiating on pus from a ruptured lung abscess, presumably formed from aspirating oropharyngeal contents in his debilitated state.

The uses of medicine and science
Franklin felt that peoples’ worth depended greatly on their contributions to others. He wrote that he believed in God, but that “the most acceptable Service we can render him is doing good to his other Children.” He realized the difficulties involved, however, for he stated, “Serving God is Doing Good to Man, but Praying is thought an easier Service, and therefore more generally chosen.” Franklin was a scrupulous, insatiably curious observer of natural phenomena, and he appreciated scientific discoveries for their own sake, but he was especially interested in their practical utility. He considered his experiments with therapeutic electricity unsatisfactory because they made no useful contributions to mankind. By such activities as promoting smallpox inoculation, developing a flexible urinary catheter for his brother, inventing bifocals, founding a hospital, and proposing potential applications of his observations on evaporative cooling and color absorption of heat, however, Franklin made important practical contributions to improve the condition of others. Moreover, his equanimity and good humor in dealing with his own illnesses provide an admirable demonstration of how to deal with chronic disease. He was thus an exemplary doctor, but these remarkable medical achievements were only a small part of his life as a printer, author, diplomat, politician, statesman, scientist, and inventor. As Carl Van Doren concluded in his biography of Franklin, “he seems to have been more than any single man: a harmonious human multitude.”

Further reading

Seal designed by Benjamin Franklin
for the Pennsylvania Hospital. Franklin chose the story of the Good Samaritan as the motif for the official Hospital seal. © Courtesy of the Pennsylvania Hospital Historic Collections, Philadelphie.

LE DOCTEUR BENJAMIN FRANKLIN ET SES DÉCOUVERTES SCIENTIFIQUES ET MÉDICALES

Benjamin Franklin prend le titre de « Docteur » après avoir reçu un titre universitaire honorifique en 1759 pour ses contributions à la compréhension de l’électricité. Malgré son absence d’études médicales formelles, il aurait pu également revendiquer ce titre en tant que médecin. En effet, il prodigua de nombreux conseils médicaux, aidant à la création d’un hôpital, réalisa des expériences médicales, inventa des instruments médicaux, encouragea la vaccination contre la variole, étudia les effets du saturnisme et soutint l’éducation médicale. En raison de ses qualités scientifiques et analytiques, Louis XVI désigna Franklin pour participer à une commission de neuf membres destinée à étudier les affirmations de Franz Mesmer sur « le magnétisme animal » et le pouvoir qu’il disait en tirer de guérir de nombreuses affections. Franklin reconnaissait l’« effet placebo » dans la réponse des patients au traitement. Ses observations sur ses propres maladies sont judicieuses, telle la première bonne description du psoriasis. Il souffrit de goutte et de calculs vésicaux, mais affronta ses infirmités avec sérénité et bonne humeur. Ces accomplissements témoignent de sa capacité intuitive perspicace et argumentée, de sa méticulosité dans l’enregistrement de ses observations, de ses analyses pénétrantes des phénomènes scientifiques et des comportements humains, mais également de son élégance dans l’adversité. À plus d’un titre, il fut un médecin exemplaire.
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