Refractory angina
Heart and Metabolism is a journal published three times a year, focusing on the management of cardiovascular diseases. Its aim is to inform cardiologists and other specialists about the newest findings on the role of metabolism in cardiac disease and to explore their potential clinical implications. Each issue includes an editorial, followed by articles on a key topic. Experts in the field explain the metabolic consequences of cardiac disease and the multiple potential targets for pharmacotherapy in ischemic and nonischemic heart disease.
EDITORIAL
Living with pain ................................................................. 2
L. H. W. Gowdak

ORIGINAL ARTICLES
Refractory angina or inappropriate antianginal therapy? ......................... 4
A. Huqi, M. Marzilli
Prevalence of refractory angina in clinical practice ................................ 9
L. H. W. Gowdak
Prognostic implications of refractory angina ....................................... 13
P. G. Steg
Nonpharmacological approaches to refractory angina ........................... 18
R. Cheng, T. D. Henry
Clinical benefits of treating angina directly at the cardiac cell level with trimetazidine ................................................................. 25
I. Milinković, A. J. Coats, G. Rosano, Y. Lopatin, P. M. Seferović

CASE REPORT
The role of optimal medical therapy in patients with refractory angina .......... 32
L. H. W. Gowdak

REFRESHER CORNER
Estimating ischemic burden ................................................................ 37
V. Agarwal, M. F. Di Carli

HOT TOPICS
Errare humanum est, perseverare autem diabolicum .............................. 44
A. Huqi

GLOSSARY ................................................................................. 47
G. D. Lopaschuk
In this issue of *Heart & Metabolism*, our attention is focused on the challenging clinical condition of refractory angina. William Heberden’s classic description of angina pectoris was first presented to the Royal College of Physicians in 1768 and a few years later published in the *Medical Transactions* of the College. Although receiving praise for his detailed description of the symptoms accompanying the natural history of patients with exertional angina, Heberden humbly acknowledged that “with respect to the treatment of this complaint, I have little or nothing to advance.” Exactly two and a half centuries later, we are awed by the great developments we have witnessed in the treatment of patients with stable angina, ranging from effective antianginal drugs to revascularization procedures (percutaneous or surgical). But despite all the advances, we are occasionally faced with a patient with disabling symptoms related to myocardial ischemia and who becomes unresponsive after an initial course of medical therapy. To make things worse, because of the anatomical complexity of the disease, including the diffuseness of the obstructive lesions, or because the patient is considered high risk, the Heart Team deems that revascularization is unsuitable, and the patient is said to have refractory angina. What happens then? The articles in this issue will give the reader a broader, updated, and (hopefully) uplifting perspective on the topic.

We start our journey questioning the definition of refractory angina in light of what is known regarding the multiple pathophysiological mechanisms involved in angina or myocardial ischemia. After reading the article by Dr Huqi and Prof Marzilli, it becomes clear that one must first understand the underlying mechanism responsible for the clinical manifestations of any disorder in order to propose an adequate therapeutic strategy. In the setting of stable angina, failing to adhere to this recommendation may lead not only to misuse of currently available pharmacological therapies, but also to overuse of myocardial revascularization procedures. In the end, many patients with apparent refractory angina may simply be undergoing inappropriate therapy.

The difficulty in making a proper diagnosis of refractory angina may help explain the uncertainties regarding the true prevalence of refractory angina in daily clinical practice, which I discuss in a following article. Even so, the estimated incidence of patients fulfilling the criteria for refractory angina per year on both sides of the Atlantic make it clear we should be prepared for a growing population of patients with difficult-to-control symptoms.

In addition to the evident impairment in quality of life that patients with refractory angina experience, persistent angina also has prognostic implications, as discussed in the article by Prof Steg. Large, contemporary registries have shown that the presence of angina and/or myocardial ischemia identifies patients at higher risk for cardiovascular events, including cardiovascular death and/or myocardial infarction. Thus, our mission has been expanded, aiming to improve symptoms and to reduce the cardiovascular risk in patients with angina and/or ischemia. As a welcomed complement to the topic, the Refresher Corner article by Prof Di Carli and Prof Agarwal presents the many clinical tools at our disposal for estimating ischemic burden. Thanks to these tools, ischemia is no longer a dichotomous variable (present/absent), but rather a quantifiable one.

The management of patients with refractory angina may seem, at first, to be a dead-end road, but it is not. There is, indeed, great opportunity for medical
research to introduce new drugs and new nonpharmacological therapies for such patients. Prof Henry’s article goes through the surprisingly many options in different stages of development for clinical use in the management of patients with refractory angina. Many of these technologies are not available in all countries (e.g., enhanced external counterpulsation [EECP]), and many are still in early phase clinical trials (such as cell-based therapies or the implantation of a coronary sinus reducer). Nevertheless, it is a comprehensive overview that serves as proof that patients with persistent angina have not been forgotten.

No matter how fascinating it may be to look at so many different new technologies being developed to manage a patient with persistent angina, we must bear in mind Prof Marzilli’s opening paper in this issue: how appropriate is antianginal therapy in a symptomatic patient? The paper by Prof Seferović and colleagues underscores the clinical benefit of treating angina directly at the level of the cardiac cell with trimetazidine. As an antianginal agent devoid of any significant hemodynamic effect, trimetazidine treats ischemia at the cellular level, regardless of the underlying mechanism of ischemia, rendering it an attractive option as add-on therapy. In line with Prof Marzilli’s advice, I share a clinical case in which the wise utilization of antianginal agents with different modes of action, according to their safety profile and tolerability, was of paramount importance in offering better symptom control in a patient initially referred to us as being refractory to medical therapy.

In the final article, with a provocative title written in Latin, Dr Huqi draws our attention to the long-standing assumption that if there’s angina, one should find the obstruction and get rid of it. With few, but strong, arguments, she does show us that the relationship between a coronary stenosis and myocardial ischemia is not always direct, meaning that we may have patients with angina and no obstructive coronary disease, and that, conversely, we may find patients with obstructive coronary disease and no angina/ischemia. It’s past time to rethink the “plumber theory” when treating a patient with stable angina.

I run a clinical program at the Heart Institute in São Paulo, Brazil for patients with refractory angina. I listen to them talking about what it is like to live with pain without any apparent perspective of relief. They live in fear and distress. They refrain from any physical effort; socialization is impaired. They have high rates of depression and anxiety. Editing this issue reminded me that just because something has never been done before, it does not mean it can’t be done. Clinical scientists are moved and touched by patients’ demands, and together with our colleagues from basic research, we all come together in search of a better understanding of the task at hand and, with that, solutions that at present are elusive.

If I could reply to William Heberden on the treatment of patients with stable angina, I’d tell him, “With respect to the treatment of this complaint, I have so much to advance.”

I hope you enjoy the reading as much as I have.
Refraclory angina or inappropriate antianginal therapy?

Alda Huqi,1 MD, PhD and Mario Marzilli,2 MD, PhD
1Cardiac Care Unit at the Santa Maria Maddalena Hospital, Volterra, Pisa, Italy
2Cardiovascular Medicine Division, Pisa University Medical School, Pisa, Italy

Correspondence: Professor Mario Marzilli, Professor and Chairman, Cardiovascular Medicine Division, Pisa University Medical School, Via Paradisa, 2, 56100 Pisa, Italy
E-mail: mario.marzilli@med.unipi.it

Abstract
Ischemic heart disease (IHD) is a main determinant of global health and mortality. Despite significant advances in therapeutic options, many patients complain with persistent symptoms and/or signs of myocardial ischemia (ie, refractory angina). Main therapeutic strategies used in angina patients aim at either reducing the effects of coronary stenosis on coronary blood flow or at removing the coronary stenosis itself. However, obstructive coronary artery disease is not synonymous with IHD. Indeed, a number of other factors can precipitate myocardial ischemia, including microvascular dysfunction, focal or diffuse spasm, and altered mitochondrial metabolism. It is therefore not surprising that therapeutic strategies that target epicardial coronary stenosis are not effective in all IHD patients. When approaching a patient with angina, the multiple pathophysiology model should be adopted at all levels, including diagnostic and treatment strategies. Angina should be considered refractory once the underlying mechanism has been identified and the targeted treatment has failed to control symptoms. This attitude could help stratify risk and augment treatment strategies, in this way optimizing resource utilization and improving cardiovascular outcome in the individual patient. ■ Heart Metab. 2017;72:4-8

Keywords: CAD; guideline-directed medical therapy; persistent angina

Introduction
Cardiovascular disease remains the main determinant of global health and mortality. The incidence of ischemic syndromes, one of the most relevant manifestations, increases with the occurrence of traditional risk factors and with age. For instance, the prevalence of angina pectoris, which constitutes the most frequent clinical presentation, increases progressively among adults aged 40 years and older, ranging from 4% to more than 11%.1 Guideline-directed medical therapy (GDMT) and myocardial revascularization represent the cornerstone therapies for ischemic heart disease (IHD) patients.2 Although significant advances have been registered for both therapeutic strategies, large clinical trials consistently report that many patients complain with persistent symptoms and/or signs of myocardial ischemia.3,9 In some prospective studies, the proportion of patients with symptom persistence despite GDMT and revascularization may be as high as 25% to 35%.10,11 Given the burden of the disease and the
Refractory angina

Refractory angina and/or ischemia can be defined as symptoms and/or signs of ischemia that are not adequately controlled with maximally tolerated GDMT and revascularization.13

GDMT includes lifestyle interventions (eg, smoking cessation), drugs for risk factor control (eg, antplatelet therapy, cholesterol-lowering agents) and drugs aiming at controlling symptoms.

In most guidelines, β-blockers (BBs) are the recommended first-line treatment for symptom control. BBs inhibit the action of endogenous catecholamines (epinephrine and norepinephrine in particular) on adrenergic receptors. Their antiangina effects are mediated through a reduction in ventricular inotropy, heart rate, and a decrease in the maximal velocity of myocardial fiber shortening, therefore keeping myocardial oxygen demand below the threshold at which angina occurs.

Calcium-channel blockers (CCBs) can be used either as an alternative to or on top of BBs. CCBs are potent coronary and systemic arterial vasodilators that reduce blood pressure, as well as cardiac contractility. CCBs bind to and inhibit L-type calcium channels and thus reduce calcium influx into cells. Intracellular calcium deprivation relaxes smooth muscle cells, causing vasodilation in the peripheral and coronary beds and increased coronary blood flow. Consequently, CCBs lower the frequency of angina and reduce the need for nitrates.

Nitrates represent another important alternative, particularly for those patients in whom a complete revascularization is not possible or whose symptoms are (at least in part) considered secondary to abnormal coronary vasomotion. Although the predominant effect of nitrates is to reduce preload—with a greater activity in venous than in arterial beds—at higher doses, a direct effect upon arteries also becomes evident and results in a reduction in blood pressure and afterload. These effects translate into reduced myocardial oxygen consumption and a higher threshold level before angina is triggered.

BBs, CCBs, and nitrates constitute the so-called traditional or hemodynamic antiangina agents. As mentioned, hemodynamic agents act by lowering rate-pressure product and/or producing systemic venodilation, thereby lowering left ventricular end-diastolic pressure and volume and reducing myocardial wall tension. Therefore, their main action mechanism is a reduction in oxygen requirements.

Drugs with alternative action mechanisms represent a second-line choice and, as such, have been given a lower class of recommendation.14 Trimetazidine acts at the mitochondrial level and exerts its action on myocardial ischemia independently from the precipitating mechanism. By preventing the deleterious effects of ischemia, trimetazidine maintains the contractile function of the cardiac cell and reduces anginal symptoms. Ranolazine acts by blocking late sodium channels leading to the lowering of abnormally high cytosolic calcium levels. Ivabradine and nicorandil are two other agents that improve angina symptoms.15,16 Ivabradine reduces heart rate without affecting contractility and atrioventricular (AV) nodal conduction and without altering hemodynamics. Nicorandil increases potassium ion conductance and induces vasodilation through smooth muscle relaxation.

If symptoms are not adequately controlled by GDMT with hemodynamic agents and with or without alternative agents (Table I), revascularization should be pursued in angina patients. However, none of the major international guidelines give clear indications on the time period for a drug therapy or combination to be considered “unsuccessful.” On the contrary, revascularization is often pursued without attempting

---

**Abbreviations**

BB: β-blocker; CAD: coronary artery disease; CCB: calcium-channel blocker; GDMT: guideline-directed medical therapy; IHD: ischemic heart disease

---

<table>
<thead>
<tr>
<th>Hemodynamic agents</th>
<th>Agents with alternative mode of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-Blockers (metoprolol, bisoprolol, carvedilol)</td>
<td>Trimetazidine</td>
</tr>
<tr>
<td>Calcium-channel blockers (verapamil, diltiazem)</td>
<td>Ranolazine</td>
</tr>
<tr>
<td>Nitrates (isosorbide mononitrate)</td>
<td>Ivabradine</td>
</tr>
<tr>
<td></td>
<td>Nicorandil</td>
</tr>
</tbody>
</table>

**Table I** Drugs in ischemic heart disease.
implementation and/or titration of adequate medical therapy, and less than half of patients directed to revascularization receive GDMT before percutaneous coronary intervention. Therefore, the rate of persistent angina despite maximally tolerated GDMT in clinical practice is not properly known.

**IHD as a multifactorial disease**

As mentioned, the two main therapeutic strategies used in angina patients aim at reducing the effects that a coronary stenosis produces on downstream flow (hemodynamic agents) or at removing the coronary stenosis itself (revascularization). This approach is based on the assumption that narrowing of the coronary artery limits resting and hyperemic coronary blood flow. However, several large-scale studies have shown that many patients with angina do not have obstructive coronary artery disease (CAD). On the other hand, most coronary atherosclerotic obstructions are clinically silent. Indeed, the effect that a stenosis produces at the level of the downstream coronary flow is not straightforward. Conversely, factors other than atherosclerotic coronary obstructions, including focal or diffuse spasm of normal or plaque-diseased arteries, and microvascular dysfunction due to activated platelets and/or release of constrictive, prothrombotic, and proinflammatory cytokines, can all precipitate myocardial ischemia. Moreover, likewise for a combustion engine with a perfect injection mechanism, a cardiomyocyte may still be unable to properly burn the fuel due to cellular dyshomeostasis with altered mitochondrial metabolism, dysfunction of extracellular matrix, barriers to oxygen transport, etc.

The concept of IHD as a multifactorial disease has been endorsed by the latest edition of the European Society of Cardiology (ESC) guidelines. However, according to the same documents, the so-called “alternative mechanisms” are considered only after epicardial stenosis has been excluded, as if coronary atherosclerosis were to confer some sort of immunity versus other causes of myocardial ischemia. The frequent observation that symptoms and/or ischemia persist even after stenosis removal strongly challenges this assumption. Indeed, patients with IHD are a heterogeneous group, including those in whom an epicardial stenosis is responsible for angina symptoms, those with vasospastic angina, and those with microvascular dysfunction, epicardial endothelial dysfunction, slow coronary flow, etc. It is therefore not surprising that therapies that target obstructive CAD only cannot control symptoms in all IHD patients.

The choice of the therapeutic strategy for controlling angina symptoms should be based on these new concepts. Indeed, although from a pathophysiological standpoint, the role of alternative factors underlying angina has been fully acknowledged, little or no progress has been made in applying these new concepts to diagnostic and therapeutic protocols.

BBs can be expected to be beneficial in patients with significant epicardial stenosis, whose symptoms are exacerbated by increased workload. Conversely, BBs can be counterproductive in patients with vasospastic angina; in such patients, nondihydropyridinic CCBs and nitrates have been shown to be particularly efficacious.

Hemodynamic agents are probably neutral in other patient subsets. Similarly, overrated use with improper selection of patients that would benefit from revascularization may have contributed to the lack of full-scale beneficial effects of angioplasty.

Patients with angina and suspected IHD should undergo a thorough evaluation irrespective of the coronary angiographic results. In patients displaying obstructive CAD, the effect that the epicardial stenosis exerts on downstream coronary flow should be assessed. Indeed, inadequate microvascular remodeling due to chronic low shear stress distal to the stenosis with decreased nitric oxide activity or a low perfusion pressure distally to a stenosis can negatively influence microvascular remodeling and the capacity of maximal vasodilation. Stenosis removal with coronary revascularization can reverse this effect, with angina patients obtaining symptom control. However, whether coronary microvascular dysfunction is a preexisting condition or is secondary to chronic flow alterations and, as such, potentially reversible cannot be determined with the current state of knowledge. In fact, among revascularized patients with persistent angina, microvascular dysfunction constitutes the most frequent underlying cause. Although a number of drugs have been tested in this setting, none have produced convincing results. Therefore, a patient with microvascular angina should not be labeled as a patient with refractory angina, but rather as a patient to whom we cannot offer appropriate therapy.
The overall unsatisfactory results of angina patients that are treated with the currently available therapeutic regimens have stimulated further research. Nevertheless, the lack of symptom control in all angina patients continues to be attributed to the inaccurate assessment of coronary plaques. As such, imaging modalities that assess anatomical and/or physiological relevance of epicardial coronary plaques are absorbing major resources. This attitude is in line with the diagnostic and therapeutic protocols outlined in contemporary guidelines that aim at identifying and treating coronary obstructions. However, this approach is in conflict with the multiple pathophysiology model for IHD and, again, explains the lack of benefit in all angina patients.

Conclusions

The inability of GDMT and revascularization to control symptoms in all patients with stable angina should not lead to an automatic labeling as “refractory angina.” When approaching a patient with angina, the multiple pathophysiology model should be adopted at all levels, including diagnostic and treatment strategies. Angina should be considered refractory once the underlying mechanism has been identified and the targeted treatment has failed to control symptoms (eg, patients with diffuse CAD, not amenable to revascularization). On the contrary, patients with angina despite currently available therapies should be considered as “patients with angina and inappropriate treatment.” This attitude could help stratify risk and augment treatment strategies, in this way optimizing resource utilization and improving cardiovascular outcome in the individual patient.

REFERENCES


Prevalence of refractory angina in clinical practice

Luis Henrique Wolff Gowdak, MD, PhD, FESC
Heart Institute (InCor), University of São Paulo Medical School, São Paulo, Brazil

Correspondence: Luis Henrique Wolff Gowdak, MD, PhD, FESC, Heart Institute (InCor), University of São Paulo Medical School, Avenida Dr. Enéas de Carvalho Aguiar, 44, São Paulo, SP – 05403-000 Brazil
E-mail: luis.gowdak@incor.usp.br

Abstract
According to the American Heart Association, an estimated 15.5 million Americans aged 20 years and over have coronary artery disease, and 8.2 million are living with angina pectoris. Despite enormous advances in medical therapy and myocardial revascularization procedures, a growing number of patients will present with disabling symptoms due to myocardial ischemia, in whom a combination of classic anti-anginal drugs and angioplasty or bypass surgery is ineffective in providing symptom relief. Those patients are usually referred to as having refractory angina. They usually suffer from poor self-perceived health status, have significant impairments in quality of life with a high incidence of depression, and represent a burden to the health care system due to significant resource utilization, including rehospitalization. Because of the variability in defining unsuitability for revascularization and the use of different medical strategies for symptom control, and with only limited clinical data available from small, observational studies, a precise estimate of the prevalence of refractory angina is not available. Nevertheless, its incidence has been estimated at between 5% and 15% of patients undergoing cardiac catheterization. Presently, the incidence of newly diagnosed patients with refractory angina in the United States is something between 50 000 to 100 000 per year. In Europe, the incidence is estimated to be at least 30 000 to 50 000 new cases per year. Because life expectancy is increasing worldwide, the number of patients who will fulfill the criteria for refractory angina is expected to increase as well. 

Keywords: optimal medical therapy; prevalence; refractory angina

According to the latest report from the American Heart Association based on data from the National Health and Nutrition Examination Survey (NHANES), 2009 to 2012, an estimated 15.5 million Americans aged 20 years and over have coronary artery disease, translating to a prevalence of 7.6% for men and 5.0% for women. Based on the same document, in 2012, there were 8.2 million Americans living with angina pectoris with an estimated incidence of 565 000 newly diagnosed cases each year. There is a strong association between aging and the prevalence of angina, as shown in Figure 1. The exact prevalence of angina in different countries across the globe is challenging to determine because of the lack of large-scale epidemiological studies. In one of the few studies that examined this issue in 52 countries in all continents, comprising more than 210 000 participants, the prevalence of angina ranged from 2.44% in Tunisia to 23.89% in Chad.
Despite enormous advances in medical therapy and myocardial revascularization procedures, a growing number of patients among those with stable angina pectoris struggle to cope with disabling symptoms caused by myocardial ischemia, in whom a combination of classic antianginal drugs and angioplasty or bypass surgery is ineffective in providing symptom relief. Those patients are usually referred to as having refractory angina.

For those patients to be labeled as “no-option” patients, a careful assessment of the relationship between disabling symptoms, objective demonstrable myocardial ischemia, and unsuitability for revascularization must be performed (Figure 2). In a small study with 44 patients with refractory angina, the nursing diagnosis of activity intolerance was positively related to a higher Canadian Cardiovascular Society functional class and lower cardiac work during a treadmill test.

The latter element to be considered in the diagnosis of refractory angina, the unsuitability for revascularization, is usually the most difficult one because it can reflect the extension of the disease, the risk profile of the patient, comorbidities, and the expertise of the health care providers in dealing with more complex, high-risk patients. For example, Atreya et al looked at predictors of medical management in patients undergoing elective coronary angiography for stable angina, and they found that the decision to proceed to percutaneous coronary intervention was largely dependent on patient and angiographic characteristics. Patients with advanced age and/or chronic kidney disease, or with distal and high-risk lesions, were more often referred for medical therapy.

Another aspect concerning the refractoriness to medical therapy is how aggressive antianginal agents are being used. Usually, antianginal therapies include a combination of hemodynamic agents like β-blockers, calcium-channel antagonists, and long-acting nitrates, agents that are widely available. Agents with different mechanisms of action can be found in some, but not all, countries; examples include trimetazidine, ivabradine, ranolazine, and nicorandil. In 136 patients who initially received a diagnosis of refractory angina, we have shown that intensive medical treatment with a combination of triple hemodynamic agents (β-blockers, calcium-channel antagonists, and long-acting nitrates) with trimetazidine and/or ivabradine was highly effective in providing angina relief: the number of angina attacks decreased from 7.8±9.4 to 3.8±5.1 and improvement in at least one Canadian Cardiovascular Society functional class occurred in half of those patients. So, a patient may be prematurely tagged as being refractory to medical therapy, even before all antianginal drugs have been used, leading to an overestimation of the number of patients with true refractory angina. One should keep in mind the concept that optimal medical therapy may be defined as the use of three or more antianginal drugs at maximally tolerated doses, including one heart rate–limiting agent and a coronary vasodilator.

Patients with refractory angina usually suffer from poor self-perceived health status, have significant impairments in quality of life with a high incidence of depression, and represent a burden to the health care system due to significant resource utilization, including rehospitalization.
left ventricular function is usually preserved in patients could impair left ventricle contractility, the long-term left ventricular function is usually preserved in patients with refractory angina.13

Because of the variability in defining unsuitability for revascularization, the use of different medical strategies for symptom control, and the limited clinical data available from small, observational studies, a precise estimate of the prevalence of refractory angina is not available.

Nevertheless, the incidence of refractory angina has been estimated at between 5% and 15% of patients undergoing cardiac catheterization.14 In a study conducted more than 20 years ago, the incidence of “no-option” patients was determined to be 11.8% on the basis of coronary anatomy, myocardial perfusion defects, and symptoms.15 Presently, the incidence of newly diagnosed refractory angina in patients in the United States is something between 50 000 to 100 000 per year.16 In Europe, the incidence is estimated to be at least 30 000 to 50 000 new cases per year.17

Although the true prevalence of refractory angina, as previously discussed, is difficult to ascertain, investigators agree that currently, up to 1.8 million individuals from the United States and more than 500 000 Canadians are estimated to have refractory angina.15 In a recent study from Brazil,16 the prevalence of moderate-to-severe angina was determined from a nationwide registry of more than 60 000 individuals. Participants were asked to answer the short version of the Rose/World Health Organization questionnaire,17 translated into Portuguese and validated in another study.18 Investigators found that the overall frequency of moderate-to-severe angina was 4.2%, more common in women (5.2%) than in men (3.0%).

Another difficult clinical scenario that may present itself as refractory angina relates to patients with angina in the absence of obstructive coronary artery disease at angiography and myocardial disease, now defined as type 1 coronary microvascular dysfunction. There is no specific therapy for this condition, so treatment approaches often remain empiric.19 Because there is no obstructive disease, revascularization procedures are not indicated, and patients should be treated medically. However, despite several different combined strategies for optimization of medical therapy, a substantial number of patients may remain symptomatic. In a study by Lamendola et al,20 the resolution of symptoms was recorded during a median follow-up of 11.5 years in 155 patients (mean age, 58.9±10 years; 40 men) with type 1 coronary microvascular dysfunction. Although obstructive coronary artery disease was excluded at baseline, 89 patients (57.8%) had to be readmitted to hospital because of recurrent angina, and coronary angiography had to be repeated at least once in 33 patients (21.3%). Symptom control was far from ideal; angina was considered to have improved over time in only 82 patients (52%), remained unchanged in 51 patients (33%), and got worse in 21 patients (14%), meaning that roughly half of patients with type 1 coronary microvascular dysfunction remained symptomatic despite treatment.

Because life expectancy is increasing worldwide, cardiologists should prepare to deal with an even larger number of patients who will fulfill the criteria for refractory angina. This is only the beginning.

REFERENCES


Heart Metab. (2017) 72:9-12


Prognostic implications of refractory angina

Philippe Gabriel Steg, MD, FESC, FACC
French Alliance for Cardiovascular Trials (FACT), a French Clinical Research Infrastructure (F-CRIN) Network, University Hospital Department for Fibrosis, Inflammation, REModeling in cardiovascular, respiratory and renal diseases (DHU FIRE), Paris, France; Paris-Diderot University, Paris, France; National Institute of Health and Medical Research (Inserm) U1148, Paris, France; Cardiology, Bichat Hospital, Public Hospitals of Paris (AP-HP), Paris, France; Imperial College, National Heart and Lung Institute (NHLI), Royal Brompton Hospital, London, UK

Correspondence: Philippe Gabriel Steg, Département de Cardiologie, Hôpital Bichat, 46 rue Henri Huchard, 75018 Paris, France
E-mail: gabriel.steg@aphp.fr

Abstract

In the current era of widespread use of myocardial revascularization, angina has not disappeared. It is a common symptom among patients with stable coronary artery disease (affecting approximately 20% of patients) and has ominous prognostic implications in terms of subsequent risk of death and myocardial infarction. It is also associated with an increased risk of hospitalization for cardiovascular reasons and, as such, with increased costs. Refractory angina, (ie, chronic angina that cannot be controlled by a combination of medical therapy, angioplasty, and bypass surgery, where the presence of reversible myocardial ischemia has been clinically established to be the cause of the symptoms) is a more limited subgroup, given the spontaneous tendency for anginal symptoms to improve over time and the existing pharmacologic armamentarium to treat symptoms. However, refractory angina remains associated with a sizeable long-term mortality, estimated at 20% over 5 years, and has an important impact on patients’ quality of life.

Heart Metab. 2017;72:13-17

Keywords: angina; ischemia; prognosis

Angina pectoris is a common symptom of coronary artery disease (CAD) and, in the past, angina relief was the main goal of treatment, as most antianginal agents did not affect long-term outcomes. However, over the past 40 years, the advent of myocardial revascularization dramatically changed the epidemiology of angina, both in terms of prevalence and prognostic implications; whereas angina was previously considered to be an “acceptable symptom” and treated with antianginal agents, in more recent years, the mere existence of angina despite medical therapy (and sometimes without a course of optimal antianginal therapy) has become a trigger for coronary angiography with a view to revascularization. At the same time, due to accumulating evidence regarding the prognostic benefit of pharmacological therapy for stable CAD, the goals of therapy have moved toward prevention of cardiovascular death and acute myocardial infarction (MI).1

Given the expanding scope of percutaneous coronary intervention, today, the only patients who have persistent angina are typically those for whom revascularization is considered unsuitable either because they have undergone previous—often multiple—revascularization procedures or because they have severe comorbidities, left ventricular dysfunction, or very extensive and complex anatomical features of CAD.
Prognosis of patients with refractory angina

There is only limited contemporary data regarding the current prognosis of patients with stable angina and even less for those patients with refractory angina. Most studies are small or relatively old with a very large range (3% to 21%) of annual mortality reported for patients with refractory angina. In addition, there are several methodological issues that make it difficult to accurately and consistently assess the prognosis of patients with angina. First, there may be a discrepancy between outcomes assessed in population series (such as the Framingham study) versus those obtained from clinical trials with highly selected participants. Furthermore, there are several definitions of angina, and though the expression “stable angina” is sometimes used to define a group of symptomatic patients with angina, it is also sometimes used to refer to patients with established CAD, distancing it from an acute coronary syndrome, regardless of symptoms. Finally, given the marked predominance of men among patients with angina, the information regarding the prognosis of angina in women is limited.

In historical series, mortality was very high; in the Framingham study, in the 1960s, 10-year mortality rates in patients with angina were approximately 40% for men aged over 50 years and women aged over 60, quite like that of patients with a previous MI. In 1988, Swedish investigators from the Multifactor Primary Prevention Trial reported that men with angina but no previous MI had a 14.1% incidence of fatal and nonfatal coronary events during 7.3 years of follow-up; the incidence was 29.4% in men with angina and previous MI. More recently, in a series of 59 patients from the Cleveland Clinic, 1-year mortality was 17%. In a series of patients undergoing

Abbreviations
BARI-2D: Bypass Angioplasty Revascularization Investigation 2 Diabetes; CAD: coronary artery disease; CLARIFY: prospective observational Longitudinal Registry of patients with stable coronary artery disease; MI: myocardial infarction; OPTIMIST: OPTions In Myocardial Ischemia Syndrome Therapy

Fig. 1 Prognosis of nitrate and test-positive angina: standardized mortality ratios for coronary heart disease, by sex, within age groups. Abbreviations: CI, confidence interval; SMR, standardized mortality ratios. After reference 9: Hemingway et al. JAMA. 2006;295:1404-1411. © 2006, American Medical Association.
coronary angiography at the Duke University, mortality was 38% at an average follow-up of 2.2 years in 487 patients who did not undergo revascularization. These figures suggest that mortality of this group may be very high and certainly higher than that of patients subjected to elective revascularization. Indeed, in another series from the Minneapolis Heart Institute, the mortality rate at 3 years for patients who underwent complete revascularization was lower than for those who underwent suboptimal revascularization or who were not amenable to revascularization (14.8% vs 6.6%, P=0.004, respectively).

A large Finnish, prospective, population-based study examined coronary mortality in ambulatory patients with angina, defined either by the prescription of nitrates or by abnormal noninvasive or invasive test results. The age-standardized annual incidence per 100 population of all cases of angina was 2.03 in men and 1.89 in women, with a sex ratio of 1.07 (95% confidence interval, 1.06-1.09). Coronary mortality was highly correlated with age (Figure 1), but in each age group, the relative increase in mortality between patients with versus those without angina was similar for men and women. In another study, angina was present in approximately half of the patients after acute coronary syndrome, and it was associated with a marked increase in the risk of hospital admission.

The prognostic importance of angina versus myocardial ischemia has been examined in several studies. In the CLARIFY registry of stable CAD patients (prospective observational Longitudinal Registry of patients with stable coronary artery disease), among more than 20,000 patients who had undergone a noninvasive test for myocardial ischemia, 65% of the patients had neither angina nor evidence of myocardial ischemia, 15% had evidence of myocardial ischemia but no angina, 9% had angina alone, and 11% had angina and ischemia. Angina, with or without ischemia, was clearly associated with higher rates of cardiovascular death or MI at follow-up, whereas silent ischemia was not (Figure 2).

Interestingly, most outcome events occurred in patients with neither anna nor evidence of myocardial ischemia, 15% had evidence of myocardial ischemia but no angina, 9% had angina alone, and 11% had angina and ischemia. Angina, with or without ischemia, was clearly associated with higher rates of cardiovascular death or MI at follow-up, whereas silent ischemia was not (Figure 2).

Finally, with respect to the outcome of patients with refractory angina, one of the most rigorous recent studies was a single-center study (the OPTIMIST program [OPTions In Myocardial Ischemia Syndrome Therapy])

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death, nonfatal MI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemia only</td>
<td>0.90 (0.68-1.20)</td>
<td>0.47</td>
</tr>
<tr>
<td>Angina only</td>
<td>1.45 (1.08-1.95)</td>
<td>0.01</td>
</tr>
<tr>
<td>Both</td>
<td>1.75 (1.34-2.23)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CV death, MI-stroke</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemia only</td>
<td>0.90 (0.70-1.15)</td>
<td>0.40</td>
</tr>
<tr>
<td>Angina only</td>
<td>1.38 (1.06-1.80)</td>
<td>0.02</td>
</tr>
<tr>
<td>Both</td>
<td>1.57 (1.23-2.01)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CV death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemia only</td>
<td>0.86 (0.58-1.27)</td>
<td>0.45</td>
</tr>
<tr>
<td>Angina only</td>
<td>1.23 (0.80-1.89)</td>
<td>0.35</td>
</tr>
<tr>
<td>Both</td>
<td>1.89 (1.33-2.70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MI*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemia only</td>
<td>0.93 (0.65-1.32)</td>
<td>0.67</td>
</tr>
<tr>
<td>Angina only</td>
<td>1.67 (1.18-2.33)</td>
<td>0.004</td>
</tr>
<tr>
<td>Both</td>
<td>1.66 (1.18-2.33)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction.


Fig. 2. Anginal symptoms during a noninvasive test are more prognostic than presence or absence of myocardial ischemia. Adjusted hazard ratios for the primary and various composite outcomes for patients with ischemia, angina, and both, relative to patients with neither angina nor ischemia. Outcomes are adjusted for age, sex, geographical region, smoking status, hypertension, dyslipidemia, and diabetes. "Indicates fatal and nonfatal.

Fig. 3. Mortality estimation in patients with refractory angina. Kaplan-Meier survival curve in 1200 patients with refractory angina from the OPTIMIST study. The upper and lower lines represent 95% confidence intervals.

Abbreviations: OPTIMIST, OPTions In Myocardial Ischemia Syndrome Therapy.

conducted at the Minneapolis Heart Institute, which enrolled 1200 consecutive patients referred from 1996 to 2001 for refractory angina or myocardial ischemia. Most of these patients had undergone previous percutaneous coronary intervention (74.4%), previous coronary artery bypass grafting (72.4%), and had had a previous MI (72.6%). Overall, during a median follow-up of 5.1 years, 20.1% of the patients died, largely (71.8%) of cardiovascular causes. Kaplan-Meier analysis yielded a mortality of 3.9% at 1 year and 28.4% at 9 years (Figure 3). The main independent predictors of all-cause mortality were age, diabetes, angina class, chronic kidney disease, left ventricular dysfunction, and congestive heart failure. These results suggest that, in the contemporary era, the actual outcome of patients with refractory angina may not be as severe as previously thought. The improvement in survival may reflect much broader use of secondary prevention and adherence to evidence-based medications (antiplatelet agents, β-blockers, statins, and renin-angiotensin antagonists), as well as aggressive risk factor modification.

Prognosis of patients with angina due to nonobstructive CAD

In most cases, angina stems from flow-limiting stenoses in the coronary arteries. However, there may be other mechanisms for angina, with different outcomes. Patients with anginal symptoms and non-invasive evidence of myocardial ischemia in the absence of obstructive epicardial CAD are referred to as having microvascular angina. Their prognosis was traditionally considered to be good, with long-term outcomes like those of the general population. However, recent studies, done largely in women, have highlighted that long-term outcomes may not be as favorable as previously thought.

Another group of interest is the patient with variant angina, typically corresponding to coronary artery spasm in angiographically normal coronary arteries. Whereas the acute episodes of spasm can be potentially lethal, the long-term outcome of these patients, once identified and treated with appropriate medical therapy, appears good, with a low long-term mortality.

Conclusion

Despite today’s widespread use of myocardial revascularization, angina has not disappeared. It is a common symptom among patients with stable CAD and has ominous prognostic implications. Despite anginal symptoms’ tendency to spontaneously improve over time and the existence of a number of pharmacologic treatments for anginal symptoms, refractory angina, a more limited subgroup, is associated with substantial long-term mortality—estimated at 20% over 5 years—and has an important impact on patients’ quality of life.

REFERENCES

14. Mozaffarian D, Bryson CL, Spertus JA, McDonell MB, Fihn...


Nonpharmacological approaches to refractory angina

Richard Cheng, MD; Timothy D. Henry, MD
Cedars-Sinai Heart Institute, Los Angeles, California, USA

Abstract
An increasing number of patients have advanced coronary artery disease with ischemic symptoms that are refractory to medical therapy and revascularization. With the increasing adoption of percutaneous revascularization of chronic total occlusions, previously nonrevascularizable vessels may now be targets for revascularization, which may change the landscape of refractory angina. Several nonpharmacological approaches to refractory angina have emerged, including novel interventional, noninvasive, neuromodulatory, and angiogenic approaches. Enhanced external counterpulsation remains the mainstay of noninvasive therapy, increasing time to exercise-induced ischemia and reducing frequency of angina episodes. Cardiac shockwave therapy is a promising noninvasive therapy, but randomized data remain limited. Neuromodulatory approaches include spinal cord stimulation, which has demonstrated a reduction in frequency of angina episodes; however, randomized, double-blind clinical trials have yielded conflicting results. Cell-based therapies have shown a reduction in angina and an improvement in exercise tolerance, but advancement of such therapies awaits adequately powered phase 3 trials. Coronary sinus reduction is a novel interventional approach in which an hourglass-shaped device is implanted in the coronary sinus, creating a narrowing that increases upstream pressure, relieving angina. The recently reported COSIRA phase 2 randomized trial showed improvements in angina class and quality of life metrics, setting the stage for a larger definitive trial. In summary, novel nonpharmacological therapies are emerging as promising options for the growing population of formerly “no-option” patients. ■ Heart Metab. 2017;72:18-24

Keywords: enhanced external counterpulsation; neuromodulation; PCI; refractory angina

Introduction

As the population ages and with improvements in outcomes for coronary artery disease (CAD), a growing number of patients experience angina that is refractory to usual attempts at revascularization and medical therapy. The term refractory angina is defined as “a chronic condition caused by clinically established reversible myocardial ischemia in the presence of CAD, which cannot be adequately controlled by a combination of medical therapy, angioplasty or coronary artery bypass graft,” and as a “debilitating disease characterized by severe, unremitting cardiac pain, resistant to all conventional treatments for CAD”\(^1,2\)

Epidemiology and natural history

Refractory angina is increasing in frequency, with angiography revealing an estimated 10% to 15% of patients with CAD that is not amenable to revascularization, resulting in an estimated prevalence of 1.8 million...
Nonpharmacological approaches to refractory angina

Patients in the United States alone.²,⁴ Potential mechanisms behind anginal pain are summarized in Figure 1.⁵ Historically, survival was reported to be poor.⁶ Outcomes from a contemporary cohort at a specialized refractory angina clinic in the United States are more optimistic, with 1-year and 9-year survival of 96.1% and 71.6%, respectively, highlighting the importance of aggressive risk factor modification, antiplatelet therapy, and the use of novel therapies.⁷

Revascularization

Stable ischemic heart disease guidelines recommend revascularization for obstructive CAD to improve symptoms that are persistent despite maximally tolerated goal-directed medical therapy (GDMT) and also for select anatomical subsets in asymptomatic patients to improve prognosis.¹,⁸ With the increasing adoption of percutaneous revascularization (ie, percutaneous coronary intervention [PCI]) of chronic total occlusions (CTO) leading to increasing success rates and safety, previously nonrevascularizable vessels are now intervenable, which may change the landscape of refractory angina management. However, randomized controlled trials (RCTs) are still needed.⁹,¹⁰

Guideline-directed medical therapy and pharmacological approaches

β-Blockers, calcium-channel blockers, and long-acting nitrates are mainstays of GDMT,¹,⁸ although their ability to demonstrably reduce ischemic burden is limited. These agents improve symptoms by reducing heart rate, blood pressure, and myocardial contractility, but are often limited by a patient’s ability to tolerate them. Ranolazine has recently been approved in the United States and appears to decrease angina in refractory angina patients.¹⁰ The pathophysiology

Abbreviations

ACC: American College of Cardiology; ACT-34: Autologous CD34+ cell Therapy; AHA: American Heart Association; CAD: coronary artery disease; CCS: Canadian Cardiovascular Society; COSIRA: CORonary Sinus Reducer for treatment of refractory Angina; CSWT: cardiac shockwave therapy; CTO: chronic total occlusion; DIRECT: Direct myocardial laser revascularization (DMR) in Regeneration of Endomyocardial Channels Trial; EARL: European Angina Registry Link; EECP: enhanced external counterpulsation; ESC: European Society of Cardiology; MACE: major adverse cardiac events; MUST-EEDCP: MULTicenter STudy of Enhanced External Counterpulsation; PCI: percutaneous coronary intervention; PMLR: percutaneous myocardial laser revascularization; QOL: quality of life; RASCAL: Effectiveness and Cost-Effectiveness of Spinal Cord Stimulation for Refractory Angina; RCT: randomized controlled trial; RENEW: Efficacy and Safety of Intramyocardial Autologous CD34+ Cell Administration in Patients With Refractory Angina; SCS: spinal cord stimulation; STARTSTIM: Stimulation Therapy for Angina RefracTory to Standard Treatments, Interventions, and Medications; TMLR: transmyocardial laser revascularization

Fig. 1 Potential mechanisms for refractory angina extend beyond epicardial coronary artery disease (CAD)—the tip of the iceberg—to microvascular dysfunction and vasospastic angina. Neurogenic, psychogenic, and mitochondrial dysfunction may further drive angina and may be potential targets for intervention. Reproduced from reference 5: Jolicoeur EM and Henry TJ. Refractory angina. In: de Lemos J and Omland T, eds. Chronic Coronary Artery Disease: A Companion to Braunwald’s Heart Disease. Elsevier Health Sciences; 2017:412-432. © 2017 Elsevier.
and clinical efficacy of established and novel pharmacological approaches to refractory angina have been previously summarized.5,10,11

**Chronic total occlusions**

CTO are occluded or near-occluded coronary blockages lasting at least 3 months. Their corresponding myocardium may be supplied by collaterals, leading to jeopardized but viable myocardium, with resultant ischemic pain. However, the occlusion may be calcified and/or have anatomy not amenable to traditional antegrade approaches. Advances in CTO PCI, including CTO-specific equipment and retrograde approaches have increased procedural success, and a recent meta-analysis of 25 nonrandomized studies and 24,486 patients suggested successful CTO PCI to be associated with lower mortality, lower risk of stroke, less need for subsequent coronary artery bypass grafting, and lower risk for major adverse cardiac events (MACE) than unsuccessful CTO PCI.9 In nine studies reporting on angina, there was less residual angina (odds ratio, 0.38; 95% confidence interval, 0.24-0.60).9 A smaller study at a single institution with propensity matching did not replicate the mortality benefit seen in the unmatched pooled study,12 and randomized data is needed. Nonpharmacological approaches to refractory angina, including CTO PCI, are summarized in Table I.

European Society of Cardiology (ESC) guidelines recommend that PCI may be considered in patients with “expected ischemia reduction in a corresponding myocardial territory and/or angina relief.”1

**Noninvasive approaches to refractory angina**

**Enhanced external counterpulsation**

A mainstay of noninvasive therapy, enhanced external counterpulsation (EECP) utilizes pneumatic cuffs around the lower extremities; the cuffs inflate during diastole, augmenting coronary blood flow, and deflate during systole, decreasing afterload. The landmark trial MUST-EECP (MUlticenter STudy of Enhanced External Counterpulsation) randomized 139 patients with refractory angina to 35 hours of active versus inactive counterpulsation. Time to exercise-induced ST-segment depression was increased, and angina was less frequent in the active counterpulsation group13; results supported by a meta-analysis of 18 nonrandomized studies including 1768 patients showed 85% of patients who underwent EECP had a reduction of at least one Canadian Cardiovascular Society (CCS) angina class.14 The anti-ischemic mechanistic benefits of EECP were further investigated in 42 patients randomized to EECP versus sham treatment. EECP improved flow-mediated dilatation of the brachial and femoral arteries and increased the endothelial-derived vasoactive agents nitric oxide and 6-keto-prostaglandin, whereas it decreased endothelin-1 and the inflammatory markers tumor necrosis factor α and high-sensitivity C-reactive protein, among others.15 Moreover, in a perfusion stress test study of 175 patients, 83% of patients had improvement in perfusion images after a 35-hour course of EECP.16 EECP is approved and reimbursed for 35 hours over 7 weeks in the United States.

American College of Cardiology (ACC) and American Heart Association (AHA) joint guidelines recommend that EECP may be considered for relief of refractory angina,8 whereas ESC guidelines recommend it should be considered.1,17

**Cardiac shockwave therapy**

Also known as extracorporeal shockwave therapy, cardiac shockwave therapy (CSWT) delivers low-energy shockwaves applied to the borders of ischemic zones under ultrasound guidance, creating mechanical stress, which may promote neovascularization. Although there have been several small RCTs, they have been limited by small sample size and lack of consistent use of sham control. In a recent meta-analysis of a mixture of randomized and nonrandomized trials, CSWT was associated with improvements in CCS angina class, quality of life (QOL) metrics, nitroglycerin dosage, New York Heart Association functional class, left ventricular ejection fraction, 6-minute walk test (6MWT), left ventricular (LV) end diastolic dimensions, and myocardial viability.18 However, there was significant heterogeneity across trials highlighting the need for more randomized data.

**Neuromodulatory approaches to refractory angina**

Patients with a prominent neurogenic component to their cardiac pain may benefit from neuromodulation, which uses chemical, mechanical, or electrical means to interrupt pain signals, with therapies ranging from noninvasive to invasive approaches.5,10
Transcutaneous electrical nerve stimulation

Low-voltage electrical currents are administered through electrodes placed on pain points and can be used to ameliorate angina before taking more definitive approaches. ESC guidelines recommend that transcutaneous electrical nerve stimulation may be considered for refractory angina, though acknowledging the evidence is very limited.17

Spinal cord stimulation

In cardiac spinal cord stimulation (SCS), a multipolar electrode is implanted in the epidural space at the

Table I  Summary of nonpharmacological approaches to refractory angina. *Randomized data, †Sham intervention control arm included

<table>
<thead>
<tr>
<th>Indication</th>
<th>Reported benefits</th>
<th>Guidelines</th>
<th>Future directions</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCI of chronic total occlusions</td>
<td>CAD; evidence of ischemia in corresponding myocardial territory; angina</td>
<td>▲ Survival</td>
<td>• ESC 2013: IIb, B</td>
</tr>
<tr>
<td></td>
<td>▼ Stroke</td>
<td>▼ CABG</td>
<td>• Randomized trials ongoing in DECISION-CTO, EURO-CTO</td>
</tr>
<tr>
<td></td>
<td>▼ MACE</td>
<td>▼ Angina</td>
<td></td>
</tr>
<tr>
<td>Enhanced external counterpulsation</td>
<td>CAD; refractory angina</td>
<td>▲ Time to exercise-induced ischemia*</td>
<td>• ACC/AHA 2012/2014: IIb, B</td>
</tr>
<tr>
<td></td>
<td>▼ Nitroglycerin use*</td>
<td>▼ Flow-mediated dilation*</td>
<td>• ESC 2013: Ila, B</td>
</tr>
<tr>
<td></td>
<td>▼ Endothelial-derived vasoactive agent profile*</td>
<td>▼ Inflammatory markers*</td>
<td>• CCS 2012: may be considered, weak, low-quality evidence</td>
</tr>
<tr>
<td></td>
<td>▼ Perfusion defect</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac shockwave therapy</td>
<td>CAD; ischemic heart disease; refractory angina</td>
<td>▼ Angina*</td>
<td>• Approved and reimbursed for 35 h over 7 weeks in the United States and parts of Europe</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▲ LVEF*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>▲ 6MWT*</td>
<td><strong>Further randomized data needed</strong></td>
</tr>
<tr>
<td>Transcutaneous electrical nerve stimulation</td>
<td>Angina</td>
<td>▼ Angina</td>
<td>• ESC 2013: IIb, C</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>Further randomized data needed</strong></td>
</tr>
<tr>
<td>Spinal cord stimulation</td>
<td>CAD; refractory angina</td>
<td>▲ Exercise capacity*</td>
<td>• ACC/AHA 2012: IIb, B</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▲ OQL*</td>
<td>• ESC 2013: Ila, B</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▼ Angina</td>
<td>• CCS 2012: may be considered, weak, moderate-quality evidence</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▼ Nitroglycerin use</td>
<td><strong>STARTSTIM and RASCAL failed to fully enroll</strong></td>
</tr>
<tr>
<td>Transmyocardial laser revascularization</td>
<td>CAD; refractory angina</td>
<td>▼ 30-d mortality*</td>
<td><strong>No further studies planned</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percutaneous myocardial laser revascularization</td>
<td>CAD; refractory angina</td>
<td>± Exercise duration*†</td>
<td><strong>Negative DIRECT phase 2 study</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>± Angina*†</td>
<td><strong>No further studies planned</strong></td>
</tr>
<tr>
<td>Coronary sinus reduction</td>
<td>CAD; refractory angina</td>
<td>± Perfusion imaging scores*†</td>
<td><strong>Successful COSIRA phase 2 study with sham control</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>± 30-d myocardial infarction*†</td>
<td></td>
</tr>
<tr>
<td>Cell-based therapies</td>
<td>CAD; refractory angina</td>
<td>▼ Angina*†</td>
<td>• CD34+: RENEW phase 3 trial terminated early for financial reasons, <strong>Meta-analysis strongly positive</strong></td>
</tr>
</tbody>
</table>
C7/T1 level near the afferent nerves. In a meta-analysis of seven RCTs encompassing 270 patients with refractory angina, SCS was compared with coronary artery bypass grafting, percutaneous myocardial laser revascularization (PMLR), and SCS off control. As compared with SCS off control, cardiac SCS demonstrated improvements in exercise capacity and QOL. However, trial heterogeneity and lack of a usual care control limited their results. In a subsequently published EARL registry (European Angina Registry Link) of 235 patients, the 121 patients with implanted devices reported fewer angina episodes, reduced nitrate use, and improved CCS angina class.

STARTSTIM (Stimulation Therapy for Angina Refractory to Standard Treatments, Interventions, and Medications), a contemporary RCT, randomized patients to high-stimulation versus low-stimulation control, but due to slow enrollment, the study was terminated early after 68 randomized patients. Although both groups saw decreases in angina episodes, the decreases were not different between groups, nor were improvements in total exercise time and time to angina onset. Similarly, RASCAL (Effectiveness and Cost-Effectiveness of Spinal Cord Stimulation for Refractory Angina) sought to randomize patients to SCS versus usual care but failed to meet enrollment targets. Of 29 randomized patients, there was a trend toward larger improvements in angina frequency and the 6-minute walk test in the SCS group.

These two recent negative RCTs have dampened the enthusiasm for cardiac SCS. ACC/AHA and ESC guidelines published before such RCT results were available both recommend that SCS may be considered for relief of refractory angina and, in the ESC guidelines, also for improving QOL.

Transmyocardial laser revascularization

Although the exact mechanism behind its efficacy is unknown, transmyocardial laser revascularization (TMLR) employs high-powered carbon dioxide or xenon monochloride lasers by thoracotomy or sternotomy to create multiple transmural channels in the LV myocardium. A recent Cochrane Review meta-analysis of seven nonblinded RCTs with 1137 patients demonstrated superiority of TMLR in reducing angina by two angina classes (43.8% versus 14.8%). However, 30-day mortality by as-treated analysis was alarmingly higher in the TMLR group (6.8%) than in the control group (0.8%). ACC/AHA guidelines recommend that TMLR may be considered for relief of refractory angina, but CCS and ESC guidelines both recommend against its use, as the risks outweigh the potential benefit.

An alternative delivery method using an endovascular catheter-based laser system showed promise in the early 2000s, and DIRECT (Direct myocardial laser revascularization (DMR) in Regeneration of Endomyocardial Channels Trial), a phase 2 multicenter RCT, enrolled 298 patients to test the efficacy of PMLR against sham control. Exercise duration, angina class, and perfusion imaging scores were not different between PMLR and sham control groups, and there was an increase in morbidity in PMLR-treated patients. It is not clear whether the lack of efficacy as compared with TMLR was due to differences in energy delivery, endocardial versus epicardial delivery, or the removal of a placebo effect when a sham control arm was used.

New intervention technique

Coronary sinus reduction

The Reducer is an hourglass-shaped device that is implanted in the coronary sinus, creating a stenosis that modulates endocardial versus epicardial flow. At 3-year follow-up in first-in-human trials, the device was shown to have maintained patency, and angina symptoms were reduced. The recently reported COSIRA (Coronary Sinus Reducer for treatment of refractory Angina) phase 2 trial was a double-blind, sham-controlled RCT randomizing 104 patients with CCS class III or IV refractory angina to treatment versus sham. At 6-month follow-up, improvement of two CCS angina classes was achieved in 35% (treatment) versus 15% (sham), and improvement of one CCS angina class occurred in 71% versus 42%. QOL metrics were also improved, along with improvements in perfusion imaging.

Cell-based therapies

Cardiovascular cell therapy is a novel approach designed to promote neovascularization and en-
doi:10.1016/j.jdm.2017.08.005

Fig. 2 Coronary sinus-reducer system (A), an hourglass-shaped metal mesh device mounted on a balloon catheter, expanded, and implanted in the coronary sinus. The vessel wall grows into the fenestrations in the metal mesh. The central orifice of the device remains patent, leading to a narrowed channel for blood flow, increased upstream pressure, and favorable coronary blood flow redistribution (B).

Nonpharmacological approaches to refractory angina

Multiple nonpharmacological therapies are emerging as promising options for what have been previously considered “no-option” refractory angina patients. EECP remains a cornerstone noninvasive therapy; meanwhile, CTO revascularization, CSWT, and SCS require further randomized data. Moreover, novel approaches in coronary sinus reduction and cell-based therapies have demonstrated promising results in rigorously conducted double-blinded, sham-controlled randomized studies, and definitive trials are urgently needed.

Future directions and conclusions

These results were maintained at 24 months, with a trend toward decreased MACE.29 The phase 3 RENEW trial (Efficacy and Safety of Intramyocardial Autologous CD34+ Cell Administration in Patients With Refractory Angina), which compared CD34+-cell injection, no intervention, or placebo injection was terminated early, unfortunately, due to financial reasons; however, it confirmed the improvements in exercise time and angina frequency seen in phase 1 and phase 2 trials.28 A definitive phase 3 trial is still needed.
REFERENCES


Clinical benefits of treating angina directly at the cardiac cell level with trimetazidine

Ivan Milinković,1 MD; Andrew J. Coats,2 MD, PhD; Giuseppe Rosano,3,4 MD, PhD; Yuri Lopatin,5 MD, PhD; and Petar M. Seferović,1,6 MD, PhD
1Department of Cardiology, Clinical Center of Serbia, Belgrade, Serbia; 2Monash and Warwick Universities, Coventry, UK; 3IRCCS San Raffaele, Rome, Italy; 4Cardiovascular and Cell Sciences Institute, St George’s University of London, London, UK; 5Volgograd Medical University, Cardiology Center, Volgograd, Russia; 6University of Belgrade School of Medicine, Belgrade, Serbia
Correspondence: Petar M. Seferović
E-mail: seferovic.petar@gmail.com

Abstract
Patients presenting with symptoms of angina and/or signs of ischemia may have no visible coronary stenosis on coronary angiography. Myocardial ischemia as a multifactorial process implies that antianginal management should not solely focus on large coronary vessels, but also on the microvessels and cardiac cells. Trimetazidine is an effective and well-tolerated anti-ischemic agent that provides symptom relief and functional improvement, and that offers cytoprotection during ischemia. It has anti-ischemic and antianginal effects directly on cardiac cells. The drug is suitable for use as a monotherapy and also as an adjunctive therapy when symptoms are inadequately controlled by nitrates, β-blockers, or calcium antagonists. Trimetazidine does not affect hemodynamic variables; it may improve left ventricular function in patients with chronic coronary artery disease or ischemic cardiomyopathy and in ischemia during percutaneous coronary intervention or coronary artery bypass grafting. According to the 2013 European Society of Cardiology (ESC) guidelines for the management of stable coronary artery disease, trimetazidine is indicated as a second-line treatment for angina/ischemia relief. In the 2016 ESC guidelines on diagnosis and treatment of heart failure, trimetazidine is considered for the treatment of stable angina pectoris with symptomatic heart failure with reduced ejection fraction. ■
Heart Metab. 2017;72:25-31

Keywords: antianginal; cardiomyocyte; trimetazidine

Introduction
Patients presenting with symptoms of angina and/or signs of ischemia may have no visible coronary stenosis on angiography. In a large registry of 398 978 patients undergoing elective invasive angiography, 37.6% of those without known heart disease had no obstructive coronary artery disease (CAD).1 In addition, the analysis of 304 stable angina patients revealed normal or near normal coronary arteriograms in 47%.2 Acetylcholine testing triggered epicardial or microvascular coronary spasm, suggesting abnormal coronary vasomotion, in nearly two-thirds of these patients.3
On the other hand, when coronary stenoses are documented, a wide variety in the severity of symptoms, exercise intolerance, and stress echo test findings may be demonstrated. Long-term follow-up studies have shown that patients with coronary stenosis and evidence of ischemia have more adverse events, a poorer quality of life, and higher mortality than those without evidence of ischemia.

Medical therapy is the mainstay of treatment of stable angina. In the Euro Heart Survey, results from the analysis of 3779 patients with stable angina confirmed that the use of antianginal medications was similar or even greater in patients undergoing coronary revascularization. Only 3% of these patients received no antianginal medication, whereas 55% had two medications, and an additional 20% had more than two. In addition, in the RITA-2 trial (second Randomized Intervention Treatment of Angina) comparing a medical strategy with percutaneous coronary intervention (PCI) in patients with stable coronary disease, 5-year follow-up showed that 70% of patients with coronary angioplasty received more than one antianginal drug. These data indicate that in patients with stable CAD, antianginal medications are clinically justified, despite the use of myocardial revascularization procedures.

Therefore, besides coronary obstruction, there are other mechanisms influencing myocardial oxygen supply and demand, resulting in ischemia. In addition to disturbances in cardiomyocyte metabolism (often deranged by comorbidities such as arterial hypertension and diabetes), microparticle embolization, and micro- and macrovascular dysfunction could also be responsible for angina symptoms and ischemia. Also, vessel stiffening, inflammation, thrombosis, and impaired angiogenesis may play a role.

Mitochondrial dysfunction and impaired energy production have been observed in various heart diseases. Increased amounts of fatty acid oxidized by the mitochondria in relation to carbohydrate oxidation can decrease cardiac efficiency and contribute to impairment of myocardial function in heart failure (HF), ischemic heart disease, and diabetic cardiomyopathies. Therefore, inhibition of mitochondrial fatty acid oxidation is a well-established target for treatment of these diseases.

The recognition of myocardial ischemia as a multifactorial process implies that antianginal management should not focus solely on large coronary vessels, but also on the microvessels and the cardiac cell. A more convenient approach would consist of a comprehensive therapeutic strategy that encompasses all causes of ischemia. Trimetazidine, a reversible competitive inhibitor of 3-ketoacyl coenzyme A thiolase, directly targets mitochondrial fatty acid oxidation enzymes, improves the function of failing hearts, and reduces rates of glycolysis and/or increases glucose oxidation, resulting in reduced proton levels.

### Abbreviations

- **CABG**: coronary artery bypass grafting
- **CAD**: coronary artery disease
- **CLASSICA**: the Most Effective Combination of Antianginal Drugs in the Treatment of Patients with Stable Angina
- **HF**: heart failure
- **LV**: left ventricular
- **LVEF**: left ventricular ejection fraction
- **PCI**: percutaneous coronary intervention
- **RITA-2**: second Randomized Intervention Treatment of Angina
- **TACT**: Trimetazidine in Angina Combination Therapy
- **TRIMPOL II**: second TRIMetazidine in POLand study
- **TRIUMPH**: TRIMetazidine MR in patients with stable angina: Unique Metabolic Pathway
- **VASCO**: Efficacy of Trimetazidine on Functional Capacity in Symptomatic Patients with Stable Exertional Angina

### Effects of trimetazidine on clinical parameters and exercise tolerance in stable angina pectoris

According to the 2013 European Society of Cardiology (ESC) guidelines for the management of stable CAD, the treatment of angina combines lifestyle changes and drug therapy with revascularization strategies. After initiation of optimal medical treatment, which includes at least one antianginal drug and drugs for event prevention, trimetazidine is indicated as a second-line treatment for angina/ischemia relief (class IIb, level of evidence B).

The efficacy of oral trimetazidine, both as monotherapy and adjunctive therapy, in patients with angina pectoris not sufficiently controlled by other antianginal agents has been evaluated in clinical trials.

Trimetazidine has anti-ischemic efficacy that is similar to that of propranolol 20 mg thrice daily. When added to standard maintenance therapy (propranolol, aspirin, and statin), trimetazidine improves angina class. This is due to a nonmechanical anti-ischemic mechanism of action, since heart rate and rate-pressure product remain unchanged in the trimetazidine group.
In clinical practice, in the large prospective CLAS-SICA study (the Most Effective Combination of Anti-anginal Drugs in the Treatment of Patients with Stable Angina) cohort of 1213 angina patients, trimetazidine on top of other standard anti-ischemic therapy significantly reduced the number of angina attacks per week regardless of the baseline antianginal therapy.\textsuperscript{13}

In the TRIUMPH trial (TRImetazidine MR in patients with stable angina: Unique Metabolic PatH), in patients with stable angina, trimetazidine added to conventional therapy decreased the number of angina attacks and use of nitroglycerin tablets per week. It also lessened physical limitation and improved angina stability.\textsuperscript{14} Furthermore, in the TACT trial (Trimetazidine

<table>
<thead>
<tr>
<th>Study</th>
<th>No of pts</th>
<th>Design</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitale et al.,\textsuperscript{13} 2013. (VASCO trial)</td>
<td>645</td>
<td>Randomized double-blind, placebo-controlled; symptomatic and asymptomatic patients with chronic ischemic heart disease. Treatment with placebo or TMZ (70 mg/d and 140 mg/d) in addition to atenolol (50 mg/d); 12-week follow-up.</td>
<td>Total exercise duration (TMZ: 6% ± 23% vs placebo: 0.7% ± 5%; P=0.0074). Time to 1-mm ST-segment depression (TMZ: 9.6% ± 33% vs placebo: 3% ± 16.8%; P=0.0239).</td>
</tr>
<tr>
<td>Makolin\textsuperscript{14} et al., 2004. (TRIUMPH trial)</td>
<td>846</td>
<td>Open-label, uncontrolled; stable angina patients. Treatment with TMZ (70 mg/d) in addition to conventional therapy; 8-week follow-up.</td>
<td>Weekly number of angina attacks (11.2 ± 0.4 to 3.6 ± 0.2; P&lt;0.0001). Weekly nitroglycerin use (11.9 ± 0.8 to 3.4 ± 0.2; P&lt;0.0001). QOL improvement (P&lt;0.0001) for all five items: Physical limitation score (0.7 ± 0.7 to 61.0 ± 0.6). Angina stability score (57.6 ± 0.9 to 92.5 ± 0.7). Angina frequency score (33.3 ± 0.7 to 55.6 ± 0.8). Treatment satisfaction score (62.3 ± 0.7 to 77.4 ± 0.5). Disease perception score (36.7 ± 0.6 to 55.5 ± 0.7). AE in 2.4% (22/906).</td>
</tr>
<tr>
<td>Chazov et al.,\textsuperscript{15} 2005. (TACT trial)</td>
<td>166</td>
<td>Randomized, placebo-controlled; stable angina patients resistant to nitrates or β-blockers. Treatment with placebo or TMZ (60 mg/d) in addition to β-blockers or long-acting nitrates; 12-week follow-up.</td>
<td>Total exercise duration (417.7 ± 14.2 s to 506.8 ± 17.7 s in TMZ vs 435.3 ± 14.8 s to 458.9 ± 16.2 s in placebo; P&lt;0.05). Time to 1-mm ST-segment depression (389.0 ± 15.3 s to 479.6 ± 18.6 s in TMZ vs 411.8 ± 15.2 s to 428.5 ± 17.3 s in placebo; P&lt;0.05). Time to onset of angiina (417.0 ± 16.9 s to 517.3 ± 21.0 s in TMZ vs 415.1 ± 16.5 s to 436.4 ± 18.5 s in placebo; P&lt;0.005). Weekly number of angina attacks (5.6 ± 0.6 to 2.7 ± 0.5 in TMZ vs 6.8 ± 0.7 to 5.1 ± 0.7 in placebo; P&lt;0.05). Weekly nitroglycerin use (5.2 ± 0.9 to 2.8 ± 0.8 in TMZ vs 5.5 ± 0.8 to 4.1 ± 0.9 in placebo; P=ns).</td>
</tr>
<tr>
<td>Szwed et al.,\textsuperscript{16} 2001. (TRIMPOL II trial)</td>
<td>347</td>
<td>Randomized, multicenter, double-blind, placebo-controlled; stable, effort-induced angina patients with documented coronary artery disease. Treatment with placebo or TMZ (60 mg/d) in addition to metoprol (100 mg/d), 12-week follow-up.</td>
<td>Time to 1-mm ST-segment depression (341 ± 114 s to 427 ± 134 s; P=0.01). Total exercise duration (420 ± 108 s to 485 ± 122 s; P&lt;0.05). Total work (8.43 ± 1.90 to 9.65 ± 2.22; P&lt;0.05). Maximum ST depression (1.67 ± 0.46 mm to 1.42 ± 0.71 mm; P&lt;0.01). Time to onset of angina (372 ± 116 s to 465 ± 124 s; P&lt;0.01). Mean weekly number of angina attacks (4.0 ± 3.2 to 2.1 ± 2.4; P&lt;0.01). Mean weekly nitrate consumption (2.8 ± 2.5 to 1.5 ± 1.9; P&lt;0.05). Angina pain intensity (Borg scale); P=ns. Rate-pressure product; P=ns.</td>
</tr>
<tr>
<td>Ruzyllo et al.,\textsuperscript{17} 2004.</td>
<td>94</td>
<td>Subgroup from TRIMPOL II; patients with history of revascularization for coronary artery disease and who are symptomatic after 6 months on metoprol (100 mg/d). Treatment with placebo or TMZ (60 mg/d) in addition to metoprol (100 mg/d), 12-week follow-up.</td>
<td>Time to 1-mm ST-segment depression (385.1 ± 144.6 s vs 465.0 ± 143.8 s; P&lt;0.01). Exercise test duration (466.9 ± 144.8 s vs 524.4 ± 131.5 s; P=0.048). Total workload (9.0 m.e. ± 2.4 m.e vs 10.1 m.e. ± 2.4 m.e; P=0.035). Time to onset of angina (433.6 ± 164 s vs 508.1 ± 132.4 s; P=0.031).</td>
</tr>
</tbody>
</table>

Table I: Trials on exercise tolerance and clinical effects of trimetazidine in stable angina patients.

Abbreviations: AE, adverse events; ns, nonsignificant; pts, patients; QOL, quality of life; TACT, Trimetazidine in Angina Combination Therapy; TMZ, trimetazidine; TRIMPOL II, second TRImetazidine in POLand study; TRIUMPH, TRImetazidine MR in patients with stable angina: Unique Metabolic PatH; VASCO, Efficacy of Trimetazidine on Functional Capacity in Symptomatic Patients with Stable Exertional Angina.
in Angina Combination Therapy), trimetazidine combined with nitrates or β-blockers improved not only angina symptoms, but also stress echo parameters.16 Similar evidence comes from trials investigating the addition of trimetazidine to β-blocker monotherapy. The VASCO-angina trial (Efficacy of Trimetazidine on Functional Capacity in Symptomatic Patients with Stable Exertional Angina) gives evidence that standard- and high-dose trimetazidine improves effort-induced myocardial ischemia and functional capacity in patients with chronic stable angina receiving atenolol.15 In the TRIMPOL II trial (second TRIMetazidine in POLand study), the combination of trimetazidine and metoprolol produced greater improvements in angina symptoms and parameters of exercise testing than metoprolol alone (Table I).17

A growing proportion of patients with stable angina require combined antianginal medications to control symptoms. Indeed, in the subpopulation of patients with a history of PCI or coronary artery bypass grafting (CABG) included in the TRIMPOL II study, trimetazidine provided antianginal efficacy in post-revascularized patients with recurrent angina despite monotherapy with metoprolol.18

A meta-analysis including 1628 patients with stable angina pectoris confirmed the efficacy of trimetazidine as an addition to conventional antianginal agents, regardless of treatment duration.19 The beneficial effects were reflected in a decrease in the number of angina attacks and a lower use of nitroglycerin, longer time to 1-mm ST-segment depression, higher total work, and longer exercise duration at peak exercise. In the meta-analysis by Danchin et al on 19 028 patients with stable angina, trimetazidine mono-therapy was comparable to non-heart-rate-lowering antianginal treatments, but was significantly better than placebo (Table II).20

### Effects of trimetazidine on left ventricular function in stable angina pectoris and ischemic heart disease

A meta-analysis of 11 randomized clinical trials of 545 patients established the efficacy of trimetazidine as monotherapy in the treatment of stable angina pectoris. Trimetazidine monotherapy improved left ventricular (LV) function compared with placebo, with an LV ejection fraction (LVEF) improvement of 6.88%, a reduction in LV end systolic volume by 11.58 mL, and a reduction in wall motion score index (WMSI) by 0.23.21

### Effects of trimetazidine in patients with ischemic cardiomyopathy

In patients with ischemic cardiomyopathy, trimetazidine treatment has been associated not only with functional improvement and reduction in hospitalizations and mortality, but also with a significant positive effect on LV remodeling.22 Trimetazidine improves LV remodeling processes, levels of natriuretic peptides and cardiac troponin, and arteriolar endothelium-dependent relaxation.23 Such results have been demonstrated only in ischemic, and not in nonischemic, HF patients.24,25

In the 2016 ESC guidelines on diagnosis and treatment of HF, trimetazidine is considered for the treatment of stable angina pectoris with symptomatic HF with reduced ejection fraction. It can be used to

<table>
<thead>
<tr>
<th>Meta-analysis</th>
<th>No of RCT/ No of pts</th>
<th>Design</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peng et al.,19 2014.</td>
<td>13 / 1628</td>
<td>TMZ combination with antianginal drugs (β-blockers and calcium-channel blockers) vs antianginal drugs alone.</td>
<td>Weekly number of angina attacks (-0.95, 95% CI: -1.30 to -0.61; P&lt;0.001). Time to 1-mm ST-segment depression (+0.30 s, 95% CI: 0.17 to 0.43; P&lt;0.001). Total exercise duration (+46 s, 95% CI: 28 to 66; P&lt;0.001). Time to 1-mm ST-segment depression (+55 s, 95% CI: 35 to 77; P&lt;0.001). Time to onset of angina (+54 s, 95% CI: 24 to 84; P&lt;0.001).</td>
</tr>
<tr>
<td>Danchin et al.,20 2011.</td>
<td>218 / 19 028</td>
<td>TMZ vs placebo. TMZ vs non–heart-rate-lowering antianginal drugs.</td>
<td>Total exercise duration (+46 s, 95% CI: 28 to 66; P&lt;0.001). Time to 1-mm ST-segment depression (+55 s, 95% CI: 35 to 77; P&lt;0.001). Time to onset of angina (+54 s, 95% CI: 24 to 84; P&lt;0.001). Weekly number of angina attacks (-0.28 s, 95% CI: -1.17 to 0.64; P=ns). Total exercise duration (+7 s, 95% CI: 12 to 28; P=ns). Time to 1-mm ST-segment depression (-1 s, 95% CI: -23 to 22; P=ns). Time to onset of angina (+8 s, 95% CI: -22 to 40; P=ns).</td>
</tr>
</tbody>
</table>

Table II Meta-analysis of randomized controlled trials on exercise tolerance and clinical effects of trimetazidine in stable angina pectoris. Abbreviations: CI, confidence interval; ns, nonsignificant; pts, patients; RCT, randomized controlled trials; TMZ, trimetazidine.
relieve angina in patients with persistent symptoms despite treatment with a β-blocker (or alternative) (class IIb, level of evidence A). This recommendation is based on drug effects to improve functional capacity, exercise duration, and LV function in patients with HF with reduced ejection fraction.

Patients with diabetic cardiomyopathy have impaired myocardial glucose handling and a more distal distribution of coronary atherosclerosis. Trimetazidine not only improves myocardial glucose utilization, but also the levels of glycated hemoglobin (HbA1c) and glycemia, and it increases forearm glucose uptake. In addition, in diabetic patients with ischemic heart disease, trimetazidine added to standard medical therapy has a beneficial effect on LV volumes and LVEF compared with placebo.

Effects of trimetazidine in patients undergoing revascularization procedures

Elderly patients have an increased incidence of ischemic dilated cardiomyopathy, often related to diffuse CAD. Adjunctive therapy with trimetazidine, added on to standard care, improves reverse remodeling and quality of life in these patients. The addition of trimetazidine to standard care therapy in elderly patients with diabetes mellitus and multivessel CAD after drug-eluting stent implantation can have a beneficial effect on recurrent angina pectoris, as well as on LV function and structure.

Furthermore, trimetazidine reduces the incidence of stent restenosis and major adverse cardiac and cerebrovascular events in patients undergoing PCI (Table III).

There is some evidence of a positive effect of trimetazidine on myocardial preservation in CABG patients. In a meta-analysis of six trials including 505 patients, preoperative trimetazidine therapy appeared to reduce ischemia-reperfusion injury during and after CABG.

Conclusions

Trimetazidine is an effective and well-tolerated anti-ischemic agent, which—in addition to providing symptom relief and functional improvement in patients with angina pectoris—has a cytoprotective action during ischemia. It has anti-ischemic and antianginal effects directly at the cardiac cell level, by optimizing adenosine triphosphate (ATP) use and relieving angina in patients with persistent symptoms despite treatment with a β-blocker (or alternative) (class IIb, level of evidence A). This recommendation is based on drug effects to improve functional capacity, exercise duration, and LV function in patients with HF with reduced ejection fraction.

Table III: Trials on left ventricular function parameter effects of trimetazidine in stable angina pectoris and ischemic heart disease.

<table>
<thead>
<tr>
<th>Study</th>
<th>No of pts</th>
<th>Design</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xu et al,26 2014.</td>
<td>700</td>
<td>Single-center, prospective, randomized, double-blind; elderly (aged 68.94 ± 3.54 years); multivessel CHD patients with DM undergoing coronary angiography. Treatment with placebo or TMZ (60 mg/d) in addition to conventional CHD treatment after DES implantation; 2-year follow-up.</td>
<td>LVEF (66.07% ± 4.04% vs 61.94% ± 3.05%; P&lt;0.01). LVEDD (48.07 ± 4.43 mm vs 51.25 ± 3.57 mm; P&lt;0.01). LVESD (30.81 ± 4.27 mm vs 33.48 ± 3.02 mm; P&lt;0.01). Recurrent angina pectoris, n (%): 102 (40.4) vs 130 (51.0); P=0.010. Angina pectoris, n (%): 72 (28.2) vs 96 (37.6); P=0.024. Silent myocardial ischemia, n (%): 88 (34.5) vs 117 (45.9); P=0.009.</td>
</tr>
<tr>
<td>Vitale et al,29 2004.</td>
<td>47</td>
<td>Randomized, controlled. Treatment with TMZ vs placebo, (mean age 78 ± 3 years); 6-month follow-up.</td>
<td>LVEF (34.4% ± 2.3% vs 27% ± 2.8%; P&lt;0.0001). LVEDD (63.6 ± 1.9 mm vs 64 ± 1.7 mm; P&lt;0.0001). LVESD (44.5 ± 1.1 mm vs 50 ± 0.8 mm; P=0.0001). Smaller wall motion score index (1.24 ± 0.12 vs 1.45 ± 0.19; P&lt;0.01). Improvement in angina and NYHA class and QOL.</td>
</tr>
<tr>
<td>Rosano et al,28 2003.</td>
<td>32</td>
<td>Randomized, parallel control, (mean age 67 ± 6 years); DM patients with ischemic cardiomyopathy. Treatment with TMZ (60 mg/d) vs placebo; 6-month follow-up.</td>
<td>LVEF improvement (5.4 ± 0.5% vs -2.4 ± 1.1%; P&lt;0.01). LVEDD (63.2 ± 2.1 mm to 58 ± 1.6 mm vs 62.4 ± 1.7 mm to 63 ± 2.1 mm; P&lt;0.01). Improvement in wall motion score index and in the E/A wave ratio.</td>
</tr>
<tr>
<td>Chen et al,31 2014.</td>
<td>635</td>
<td>Randomized, open; patients with DES (on TMZ for at least 30 days after stent implantation). Treatment with TMZ vs control; 1-year follow-up.</td>
<td>Lower incidence of stent restenosis (4.2% vs 11.1%; P=0.001). Higher LVEF (65.4 ± 10.7 vs 63.1 ± 10.4; P=0.006). Lower incidence of MACCEs (6.1% vs 10.8%; P=0.032). TMZ predictor for stent restenosis (OR: 0.376, 95% CI: 0.196 to 0.721; P&lt;0.003).</td>
</tr>
</tbody>
</table>

Abbreviations: CHD, coronary heart disease; CI, confidence interval; DES, drug-eluting stent; DM, diabetes mellitus; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; MACCEs, major adverse cardiac and cerebrovascular events; NYHA, New York Heart Association; OR, odds ratio; pts, patients; QOL, quality of life; TMZ, trimetazidine.
opposing deleterious effects of ischemia, maintaining the contractile myocardial function. The drug is suitable for use as monotherapy in patients with angina and as an adjunctive therapy where symptoms are not controlled by nitrates, β-blockers, or calcium antagonists. Trimetazidine does not affect hemodynamic variables, such as heart rate, systolic blood pressure, and the rate-pressure product. In addition, there is some evidence suggesting trimetazidine may improve LV function in patients with chronic CAD or ischemic cardiomyopathy and in patients experiencing ischemia during PCI or CABG.

REFERENCES


26. Ponikowski P, Voors AA, Anker SD, et al; Authors/Task Force Members; Document Reviewers. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Associa-
treating angina at the cardiac cell level: trimetazidine


The role of optimal medical therapy in patients with refractory angina

Luis Henrique Wolff Goudak, MD, PhD, FESC
Heart Institute (InCor), University of São Paulo Medical School, São Paulo, Brazil

Correspondence: Luis Henrique Wolff Goudak, MD, PhD, FESC, Heart Institute (InCor), University of São Paulo Medical School, Avenida Dr. Enéas de Carvalho Aguiar, 44, São Paulo, SP – 05403-000 Brazil
E-mail: luis.gowdak@incor.usp.br

Abstract
The management of patients with refractory angina poses a major clinical challenge. Optimal medical therapy (OMT) is of paramount importance to improving quality of life by reducing (as much as possible) the number of angina attacks with a correspondent increase in exercise tolerance. For that, a judicious use of a combination of all agents currently approved in the management of patients with stable angina should be implemented. Guidelines usually recommend a combination of hemodynamic agents, such as β-blockers, calcium-channel blockers, and/or long-acting nitrates, at maximally tolerated doses, followed by the addition (as needed) of antianginal agents with different modes of action, such as trimetazidine, ivabradine, ranolazine, nicorandil, perhexiline, allopurinol, and/or fasudil (where available). Here, we describe the case of a patient who initially received a diagnosis of refractory angina and in whom OMT greatly helped to improve symptoms. ■ Heart Metab. 2017;72:32-36

Keywords: angina; coronary artery disease; treatment

The management of patients with refractory angina poses a major clinical challenge. Because of advanced coronary artery disease (CAD), those patients are deemed to be unsuitable for myocardial revascularization procedures, which makes the role of optimal medical therapy (OMT) of paramount significance. The main goals when treating such patients are directed toward an improvement in quality of life, which can be achieved by a reduction (as possible) in the number of angina attacks with a correspondent increase in exercise tolerance.

Although no medical therapy has been specifically conceived for patients with refractory angina, a judicious use of a combination of all agents currently approved in the management of patients with stable angina should be implemented. The more conventional approach is to initially offer a combination of hemodynamic agents, such as β-blockers, calcium-channel blockers (CCB), and/or long-acting nitrates (LAN), at maximally tolerated doses. A limiting factor to a greater use for the above combination is that it can lead to a significant drop in arterial blood pressure (BP), with hypotension-related symptoms developing afterwards; additionally, other side effects, including headache, flushing (LAN and CCB), fatigue, depression, weakness, insomnia (β-blockers), swollen ankles, constipation, or flushing (CCB) may also occur. In the COURAGE trial (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation), for instance, at 3 years of follow-up, roughly 40% of patients were still complaining of angina, regardless of which arm of the trial they were assigned to (OMT...
Optimal medical therapy in refractory angina with or without percutaneous coronary intervention.\(^3\) At the same time point, in patients in the OMT-only group, 86% were taking β-blockers, 50% a CCB, and 61% a LAN.\(^4\) To answer the question of why investigators did not increase the use of those agents to a greater extent if patients were still symptomatic, one must look at the BP: at 123±0.78/70±0.52 mm Hg, BP most likely prevented any further attempt to adjust therapy.\(^4\) Moreover, for patients with stable CAD and hypertension, a systolic BP under 120 mm Hg and diastolic BP under 70 mm Hg have each recently been shown to be associated with adverse cardiovascular outcomes, including mortality.\(^5\) Therefore, if a patient is already being treated with a hemodynamic agent (alone or in combination) and remains symptomatic, one should consider OMT with antianginal agents devoid of a BP-lowering effect. Non–BP-lowering antianginal agents are trimetazidine, ivabradine, ranolazine, nicorandil, perhexiline, allopurinol, and fasudil\(^2\) (Table I). However, availability and clinical indications of those agents vary from country to country.

Another important aspect to take into consideration is whether left ventricular systolic dysfunction is present, as some antianginal agents are contraindicated in patients with angina and left ventricular dysfunction—examples include diltiazem and verapamil—or their safety has not been properly assessed in this population.

This article presents a clinical case that highlights the role of OMT in the management of a patient who initially received a diagnosis of refractory angina, and illustrates the rationale for a specific combination of antianginal agents in this scenario.

**Clinical case**

A 73-year-old man was referred to our outpatient clinical center for persistent angina due to advanced CAD. He had a long history of hypertension and type 2 diabetes mellitus. Stable CAD was diagnosed at the age of 56, and he was managed medically until the age of 63, when he suffered an acute myocardial infarction and, because of severe multivessel disease, he underwent a triple bypass surgery. He did quite well after the procedure and was asymptomatic without any functional limitation until 6 months ago, when angina relapsed and became progressively limiting. He was unable to perform any ordinary activity without pain, for which a short-acting nitrate was frequently taken. When first seen in another health facility, his heart rate (HR) was 80 beats per minute (bpm) and BP, 144/78 mm Hg. Findings on physical examination were unremarkable. He was on metoprolol succinate 50 mg/day, atorvastatin 80 mg/day, aspirin 100 mg/day, and perindopril 8 mg/day. Electrocardiography revealed abnormal Q waves in DII, DIII, and aVF. An echocardiogram showed a mildly enlarged left ventricle (left ventricular end diastolic diameter, 58 mm) with a moderately depressed left ventricular function (left ventricular ejection fraction, 40%). Metoprolol succinate was increased to 100 mg/day. On his next ap-
pointment, he complained of experiencing ten angina attacks per week; he was feeling fatigued but with no shortness of breath. HR dropped to 72 bpm and BP to 136/72 mm Hg. Amlodipine 5 mg daily was added to his treatment regimen. One month later, he did not notice much improvement; angina was still bothering him with an average of eight attacks per week. HR remained unchanged at 74 bpm and BP further decreased to 128/66 mm Hg. Isosorbide-5-mononitrate 20 mg twice daily was added to his treatment regimen. Two weeks later, he was brought to the emergency department after losing consciousness for about 3 minutes. Electrocardiography revealed his heart was in sinus rhythm with a HR of 80 bpm and no acute ischemic abnormalities; troponin levels were normal. BP was low at 96/50 mm Hg. Nitrates were discontinued, and because of persistent angina with a poor response to medical therapy, a coronary angiography was ordered (Figure 1). A heart team was consulted; because of the extension and diffuseness of the disease, he was not considered a good candidate for another revascularization procedure and was referred to our center for further evaluation.

At his first appointment in our facility, his disease was still considered to be Canadian Cardiovascular Society (CCS) class III-IV, he was on metoprolol succinate 100 mg/day + amlodipine 5 mg/day, and he had a resting HR of 68 bpm and a BP of 124/60 mm Hg. Trimetazidine 35 mg twice daily was added to his treatment regimen. One month later, angina had improved from eight episodes per week to four, and he could walk briskly in the park without pain. His level of fatigue had improved as well. His vitals showed a HR of 72 bpm and a BP of 126/68 mm Hg. At that point, ivabradine 5 mg twice daily was added to his treatment regimen.

At a follow-up visit, at which he had a HR of 68 bpm and no change in BP, ivabradine was uptitrated to 7.5 mg twice daily. When last seen, he could resume most of his daily activities without pain. Occasionally, angina recurred during more strenuous activities, but this was easily relieved by a short-acting nitrate. Another echocardiogram performed 6 months after OMT showed an increase in left ventricular ejection fraction from 40% to 46%. Figure 2 shows the process of optimization of medical therapy in this patient who initially received a diagnosis of refractory angina.

Discussion

This case illustrates that OMT can improve the quality of life, decrease the number of angina attacks, and increase exercise tolerance in patients who initially receive a diagnosis of refractory angina and have no perspectives for myocardial revascularization procedures, as our group has previously shown. The decision-making process in this patient followed the more common approach adopted in many international guidelines for the management of patients with stable angina, which state that a combination of β-blocker and CCB should be considered initially. If patients remain symptomatic, LAN should be considered along with other non–BP-lowering agents. In this symptomatic patient on metoprolol + amlodipine, severe hypotension developed after the introduction of LAN, and angina could not be adequately controlled. Ranolazine has not been recommended to be used in patients with angina and left ventricular systolic dysfunction because of the lack of

**Fig. 1** Left panel shows the left coronary artery system with left anterior descending (LAD) artery occlusion after the first septal branch and multiple obstructive lesions in the left circumflex (LCX) artery territory. Center panel shows the occluded right coronary artery (RCA). No grafts were visible except for a left internal mammary artery (LIMA)-LAD seen in the right panel. Note the diffuse atherosclerosis from proximal to distal beds, leading to a thread-like appearance with small distal runoff in the LAD. Other abbreviation: OM, obtuse marginal branches.
Optimal medical therapy in refractory angina

Fig. 2 Optimal medical therapy in a patient with persistent angina unsuitable for revascularization. Abbreviations: BP, blood pressure; bpm, beats per minute; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CCS, Canadian Cardiovascular Society classification; HR, heart rate; LVEF, left ventricular ejection fraction; MI + 3-VD, myocardial infarction + three-vessel disease.

In conclusion, in this nonrevascularizable patient with persistent angina, the combination of conventional antianginal agents (β-blockers and CCBs) with non–BP-lowering agents (trimetazidine and ivabradine) provided an excellent control of angina and increase in exercise tolerance, with good tolerability and no side effects.

REFERENCES

Optimal medical therapy in refractory angina


Ischemic heart disease (IHD) remains the leading cause of death in the world. Although the role of anatomically guided early revascularization is firmly established in patients with acute coronary syndromes, its role in patients with stable IHD is more controversial. Indeed, in randomized controlled trials in patients with stable IHD, revascularization based on anatomic thresholds has not resulted in lower rates of adverse cardiovascular events than guideline-directed medical therapy\(^1\)\(^2\) or fractional flow reserve–guided percutaneous intervention\(^3\). An alternative approach generated from observational\(^4\) and post hoc\(^5\) analyses proposes that there may be a threshold of inducible ischemia above which an early revascularization strategy could result in improved cardiovascular outcomes. This suggests that a binary approach based on the assessment of the presence or absence of ischemia would be insufficient and that quantification of total ischemic burden is essential for selecting patients with stable IHD for revascularization.

**Noninvasive quantification of ischemic myocardium**

**Radionuclide myocardial perfusion imaging**

Single-photon emission computed tomography (SPECT) and positron emission tomography (PET) are the two nuclear medicine–based approaches for evaluation of ischemia by myocardial perfusion imaging (MPI). The basic principle of radionuclide MPI for detecting obstructive coronary stenosis and quantification of ischemic myocardium is based on the estimation of perfusion deficit that results from impaired coronary flow reserve (CFR). The assessment of ischemic burden is critical for selecting patients for revascularization.
ability of a radiotracer to identify a transient regional perfusion deficit in a myocardial region subtended by a coronary artery with a flow-limiting stenosis. A reversible perfusion defect is indicative of ischemia, whereas a fixed perfusion defect generally reflects scarred myocardium from previous infarction (Figure 1). Generally, myocardial perfusion defects during stress develop downstream from epicardial stenosis with greater than 50% luminal narrowing and become progressively more severe with increasing degree of stenosis. It is noteworthy that coronary stenoses of intermediate severity (eg, 50%-90%) associate with significant variability in the resulting maximal coronary blood flow, which in turns affects the presence and/or severity of regional perfusion defects.

Regional myocardial perfusion is usually assessed by semiquantitative visual analysis of the rest and stress images. The segmental scores are then summed into global scores that reflect the total burden of ischemia and scar in the left ventricle. Objective quantitative image analysis is a helpful tool for a more accurate and reproducible estimation of total defect size and severity, and it is generally used in combination with semiquantitative visual analysis (Figure 2). The semiquantitative (visual) and quantitative scores of ischemia and scar are linearly related to the risk of adverse cardiovascular events and are useful in guiding patient management, especially in assessing the need for revascularization and the response to medical therapy. The presence of transient left ventricular (LV) dilation during stress imaging (so-called transient ischemic dilation or TID) is an ancillary marker of risk that reflects extensive subendocardial ischemia and often accompanies radionuclide MPI studies with extensive and severe perfusion abnormalities (Figure 1). It is often an important finding, particularly when it occurs in patients with no or only mild perfusion abnormalities, suggesting the presence of more extensive balanced subendocardial ischemia. The presence of this abnormality has often been shown to be a harbinger of increased risk. Similarly, the presence of transient pulmonary radiotracer retention and right ventricular uptake during stress along with a drop in LV ejection fraction (LVEF) after stress (a sign of post-ischemic stunning) are also markers of multivessel LV ischemia (Figure 1).
Echocardiography

The hallmark of myocardial ischemia during stress echocardiography is the development of new regional wall motion abnormalities and reduced systolic wall thickening. Stress echocardiography can be performed in conjunction with exercise or dobutamine stress. Stress echocardiography is best at identifying inducible wall motion abnormalities in previously normally contracting segments. In a patient with wall motion abnormalities at rest, the specificity of stress echocardiography is reduced, and worsening regional function of a previously abnormal segment might reflect worsening contractile function in the setting of increased wall stress rather than new evidence of inducible ischemia. The advantages of stress echocardiography over other stress imaging techniques include its widespread availability, no use of ionizing radiation, and relatively low cost. However, there are a number of limitations for stress echocardiography, including the following: (i) there are technical challenges associated with image acquisition at peak exercise because of exertional hyperpnea and cardiac excursion; (ii) sensitivity may be limited by rapid recovery of wall motion abnormalities, which can be seen with mild ischemia, especially with one-vessel disease; (iii) detection of residual ischemia within an infarcted territory may be difficult because of an abnormality in resting wall motion; (iv) the technique for acquisition of echocardiographic data and analysis of images is highly operator dependent; and (v) complete images of good quality for viewing all myocardial segments are obtained in only 85% of patients. Newer techniques, including second harmonic imaging and the use of intravenous contrast agents improve image quality, but their effect on diagnostic accuracy has not been well documented. The use of intravenous contrast agents may also allow assessment of myocardial perfusion, although this is not approved or generally reimbursed, and data concerning the utility of contrast perfusion echocardiography are limited. As with radionuclide MPI, stress echocardiography is often used for risk stratification in patients with suspected or known IHD. A negative stress echocardiogram result is associated with an excellent prognosis, allowing identification of patients at low risk. Conversely,

**Fig. 2** Polar map of a 72-year-old patient undergoing a rest-stress positron emission tomography, showing stress (top), rest (middle), and reversibility (bottom) plots. There is a medium-sized area of previous myocardial infarction, which involves 17% of the left ventricular mass in the distribution of the left circumflex territory, with a mild amount of residual stress-induced peri-infarct ischemia. **Abbreviations:** LAD, left anterior descending artery; LCX, left circumflex artery; Nml, normal; RCA, right coronary artery; Revers, reversibility; RstCTAC, rest computed tomography attenuation correction; StrCTAC, stress computed tomography attenuation correction; TOT, total.
the risk of adverse events increases with the extent and severity of wall motion abnormalities on stress echocardiography.

Cardiac magnetic resonance

The two approaches used with cardiac magnetic resonance (CMR) to evaluate patients with known or suspected IHD include the assessment of regional myocardial perfusion (the most common clinical approach) or wall motion at rest and during stress, the latter being analogous to stress echocardiography. Whereas treadmill or bicycle exercise stress CMR is practiced in a small number of specialized centers, the logistics for stress magnetic resonance imaging (MRI) studies currently require the use of pharmacologic stress agents, including vasodilators or dobutamine. Myocardial perfusion is evaluated by injecting a bolus of a gadolinium-based contrast agent, followed by continuous data acquisition as the contrast passes through the cardiac chambers and into the myocardium. Qualitative or quantitative analysis of rapidly acquired, sequential images (a “cine loop”) obtained during the first pass of contrast into the myocardium can identify perfusion defects present at rest or under pharmacologically induced vasodilation. Relative perfusion deficits are recognized as regions of low signal intensity (black) within the myocardium (Figure 3). Stress CMR perfusion has better diagnostic accuracy than stress echocardiography and SPECT, and comparable accuracy to that obtained by PET. Quantification of ischemic burden with CMR perfusion is more challenging than radionuclide MPI because of the limited sampling of the left ventricle, which is restricted to three short-axis slices. The addition of the information from late gadolinium enhancement imaging allows differentiation between hypoperfused (potentially ischemic) and infarcted myocardium. As with other imaging modalities, there is evidence that ischemia measurements derived from stress CMR studies also have prognostic value. In line with the nuclear and echocardiography literature, a normal result on CMR study is associated with a good prognosis. Conversely, the presence of new wall motion abnormalities, regional perfusion defects, the combination of wall motion abnormalities and perfusion defects, and the presence of late gadolinium enhancement are all predictors of adverse events.

Computed tomography

Preliminary studies indicate that contrast-enhanced computed tomography (CT) might be useful to visualize myocardial perfusion, thereby enabling quantification of ischemic burden. As with stress perfusion MRI, this technique is based on acquiring CT images during the first pass of iodinated contrast into the myocardium. When the myocardium is visualized appropriately, areas of hypoenhancement correspond with perfusion defects (Figure 4). When seen under resting conditions, such defects represent areas of previous myocardial infarction, particularly if they are also associated with wall thinning or intramyocardial calcification. When CT images are acquired during administration of vasodilators, such as adenosine,
areas of inducible ischemia can be visualized. Limitations of this technique include motion-related and beam-hardening artifacts that can mimic areas of myocardial hypoenhancement. Although this technique remains experimental, the prospect of being able to perform a single scan that combines the anatomical information provided by coronary CT angiography (CCTA) with concomitant assessment of myocardial perfusion during pharmacologic stress is of potential clinical value. Recent relatively large clinical trials have shown that the technique is feasible and has reasonable diagnostic accuracy for identification of flow-limiting coronary stenoses.\(^\text{10}\)

An alternative approach to the evaluation of flow-limiting stenosis is the use of CCTA data acquired at rest (without the use of adenosine-stimulated hyperemic challenge as is performed in the catheterization laboratory) to solve numerous fluid dynamics equations to noninvasively estimate lesion-specific fractional flow reserve (so-called FFR\(_{\text{CT}}\)). Studies to date have shown only modest results with regard to the incremental value that the FFR\(_{\text{CT}}\) information adds to CCTA data. First, the DISCOVER-FLOW study (Diagnosis of ISChemia-causing stenoses Obtained Via noninvasivE Frational FLOW reserve) demonstrated that the addition of FFR\(_{\text{CT}}\) to CCTA did not improve the sensitivity for detection of lesions with an invasive FFR value under 0.8 (91\% for CCTA alone versus 88\% for CCTA + FFR\(_{\text{CT}}\)) but did improve the specificity of CCTA alone from 40\% to 82\%. Next, the DeFACTO study (Determination of Fractional flow reserve by Anatomic Computed Tomographic angiography) similarly demonstrated that sensitivity for detection of stenoses with an invasive FFR value under 0.8 remained comparable for CCTA alone versus CCTA + FFR\(_{\text{CT}}\) (84\% versus 90\%), but specificity only marginally improved from 42\% to 54\%, and the study did not reach its prespecified primary end point for improving specificity. The most recent study, NXT (Analysis of Coronary Blood Flow Using Coronary CT Angiography: NeXt sTeps), showed a sensitivity of 94\% versus 86\% for CCTA alone versus CCTA + FFR\(_{\text{CT}}\) and specificity of 34\% versus 79\%, respectively. The NXT study is an encouraging improvement to CCTA alone, but essentially demonstrates an accuracy of FFR\(_{\text{CT}}\) now approaching SPECT or stress echocardiography, although potentially inferior (without direct comparison) to stress MRI or PET.

### Table I

<table>
<thead>
<tr>
<th>Assessment of ischemic burden</th>
<th>Stress ECG</th>
<th>Nuclear SPECT</th>
<th>Nuclear PET</th>
<th>Stress echocardiogram</th>
<th>CCTA</th>
<th>Cardiac MRI perfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>++</td>
<td>86%</td>
<td>90%</td>
<td>80%</td>
<td>94%</td>
<td>84%</td>
</tr>
<tr>
<td>Specificity</td>
<td>++</td>
<td>74%</td>
<td>89%</td>
<td>86%</td>
<td>82%</td>
<td>85%</td>
</tr>
<tr>
<td>Prognosis</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Radiation</td>
<td>-</td>
<td>+++</td>
<td>+++</td>
<td>-</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Cost</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
</tr>
</tbody>
</table>

**Assessment of ischemic burden**

- Cannot be assessed
- Semiquantitative assessment with SSS and SDS; automated quantification with TPD and TID ratio
- Semiquantitative and automated quantification similar to SPECT; MBF and CFR quantification
- Semiquantitative assessment with wall motion score index and number of ischemic segments
- FFR\(_{\text{CT}}\), Stress CTP

**Future directions**

- Incorporation of Ca score
- MBA and CFR assessment, CTAC, low radiation dose protocol, stress only protocol
- New radiotracers – to facilitate exercise PET and wider use without need for on-site cyclotron, increasing application of CFR
- Myocardial perfusion, strain, single-beat 3D acquisition
- Further validation of data with Stress CTP; wider availability of FFR\(_{\text{CT}}\)
- Less laborious post processing involving quantitative and semiquantitative techniques; coronary plaque visualization

**Table I** Summary of different noninvasive imaging modalities to assess for underlying ischemia.

**Abbreviations:** Ca, calcium; CCTA, coronary computed tomography angiography; CFR, coronary flow reserve; CTAC, computed tomography attenuation correction; ECG, electrocardiogram; FFR\(_{\text{CT}}\), computed tomography-based fractional flow reserve; MBF, myocardial blood flow; PET, positron emission tomography; SDS, sum different score; SPECT, single-photon emission computed tomography; SSS, sum stress score; Stress CTP, stress computed tomography perfusion; TID, transient ischemic dilation; TPD, total perfusion defect.
Table I summarizes the different noninvasive imaging modalities to assess underlying ischemia. When interpreting this table, it is important to keep in mind that with any imaging modality, the diagnostic accuracy of the test is limited by posttest referral bias, which may increase the sensitivity and decrease the specificity of the test.

**Coronary flow reserve**

Myocardial blood flow (in mL/min/g of myocardium) and coronary flow reserve (CFR; defined as the ratio between peak stress and rest myocardial blood flow) are important physiologic parameters that can be measured by routine postprocessing of myocardial perfusion PET and CMR images. However, cardiac PET is considered the gold standard for quantifying myocardial blood flow and CFR and shows excellent accuracy and reproducibility. Pathophysiologically, CFR estimates provide a measure of the integrated effects of epicardial coronary stenoses, diffuse atherosclerosis and vessel remodeling, and microvascular dysfunction on myocardial perfusion; as such, the value obtained is a more sensitive measure of myocardial ischemia. In the setting of increased oxygen demand, a reduced CFR can upset the supply-and-demand relationship and lead to myocardial ischemia, subclinical LV dysfunction (diastolic and systolic), symptoms, and death. These measurements of CFR have important diagnostic and prognostic implications in the evaluation and management of the patients with known or suspected IHD.

Because quantitative measures of CFR integrate the fluid dynamic effects of atherosclerosis throughout the coronary arterial tree, including epicardial stenoses with early changes to endothelial and/ or smooth muscle function, it may be a superior measure of overall vascular health, providing unique information about clinical risk. Five studies have demonstrated that PET measures of CFR improve cardiac risk assessment. In the largest of these studies, CFR was prognostically important after adjusting for multiple factors, including LVEF at rest and conventional measures of ischemia. The lowest tertile of CFR had a hazard ratio of 5.6 and the middle tertile had a hazard ratio of 3.4. These results were confirmed by a similar study in a smaller cohort with a follow-up period of slightly more than a year. As discussed, the noninvasive PET measure of CFR can improve risk classification, especially among high-risk cohorts (eg, diabetics, non–ST-segment elevation myocardial infarction, in patients with chronic renal impairment, and in those with high coronary calcium scores).

Thus, assessment of CFR appears to permit a level of risk assessment beyond that achieved previously, with the potential for incorporation of vascular/endothelial status into routine patient investigations. Importantly, an abnormal CFR identified an increased risk of cardiac death even among those with normal scans by semiquantitative visual analysis. These findings suggest that coronary microvascular dysfunction is a widespread finding and that future work is needed to identify its putative role as a therapeutic target.

**Summary**

Identification and quantification of ischemic burden plays a pivotal role in guiding patient management. There are several noninvasive imaging approaches for the quantification of ischemic myocardium, each with their own strengths and weaknesses. Stress CMR perfusion and PET are the most accurate techniques. The added advantage of PET is the routine assessment of quantitative myocardial blood flow and CFR, which are integrated into clinical workflow. There is emerging evidence suggesting that in comparison with conventional ischemia assessment, CFR—a more sensitive marker of ischemia—provides incremental risk stratification and the potential for more accurate selection of revascularization candidates.

**REFERENCES**

5. Shaw LJ, Berman DS, Maron DJ, et al; COURAGE Investigators. Optimal medical therapy with or without percutaneous coronary intervention to reduce ischemic burden: results from the Clinical Outcomes Utilizing Revascularization and Aggres-


Errare humanum est, perseverare autem diabolicum

Alda Huqi, MD, PhD
Cardiac Care Unit at the Santa Maria Maddalena Hospital, Volterra, Pisa, Italy

Correspondence: Dr. Alda Huqi, MD, PhD, Cardiac Care Unit at the Santa Maria Maddalena Hospital, Borgo San Lazzerro n. 5, Volterra, Pisa, Italy
E-mail: al.huqi@gmail.com

Abstract
The initial evaluation of patients with suspected chronic angina is supported by the use of noninvasive tests and risk stratification models, which aim to identify obstructive coronary artery disease (CAD). Therefore, comparative effectiveness trials, testing the ability of a noninvasive strategy to increase the diagnostic yield for obstructive CAD have drawn increasing interest. However, after an initial increase in the diagnostic yield, there remains a significant discrepancy in results from noninvasive tests and those from coronary angiography, the latter being considered the gold standard technique for diagnosing CAD. These findings are in line with the new paradigm for ischemic heart disease, with obstructive CAD considered only one among many other determinants. With that in mind and given also the low, but persistent, risk for adverse events and the increasing costs associated with invasive management, is it appropriate to continue investing major research efforts on the development of a strategy that identifies and removes obstructive CAD?

Keywords: comparative effectiveness of noninvasive diagnostic strategies; coronary artery disease; ischemic heart disease; percutaneous coronary intervention
to 29%), underwent MPS if the pretest likelihood for obstructed CAD was intermediate (30% to 60%), or were directly sent to coronary angiography if the likelihood for obstructed CAD was high (61% to 90%). Patients randomized to the CMR-directed–care and MPS-directed–care groups underwent initial evaluation with CMR and MPS, respectively, and those with positive results were directed to coronary angiography. The primary end point was unnecessary coronary angiography, defined as a normal fractional flow reserve value (or computed angiographic assessment) for all vessels of 2.5 mm or more in diameter. At 12 months from inclusion, 42.5% of patients receiving NICE-guidelines–directed care underwent coronary angiography (34% because of a pretest likelihood of >61%, and the remaining because of a positive test result or physician judgment). The initial test result was deemed positive in 12.4% of patients in the CMR group and 18.2% of patients in the MPS group, respectively, and 17.7% and 16.2% of them underwent coronary angiography. An unnecessary angiography was performed in 28.8% of patients included in the NICE-guidelines–directed care underwent coronary angiography (34% because of a pretest likelihood of >61%, and the remaining because of a positive test result or physician judgment). The initial test result was deemed positive in 12.4% of patients in the CMR group and 18.2% of patients in the MPS group, respectively, and 17.7% and 16.2% of them underwent coronary angiography. An unnecessary angiography was performed in 28.8% of patients included in the NICE-guidelines–directed–care group, 7.5% of patients in the CMR-directed–care group, and 7.1% of patients in the MPS-directed–care group. There was no significant difference in revascularization rates or major cardiovascular events between the three groups. Authors concluded that investigation by CMR and MPS resulted in a lower probability of unnecessary angiography as compared with NICE-guidelines–directed care.

The use of CMR and MPS significantly lowered the rate of negative coronary angiograms in the CE-MARC 2 study; however, when considering only the patients undergoing coronary angiography, the results are not that gratifying. Indeed, the rate of unnecessary angiography was 67.6% (69 of the 102 patients undergoing coronary angiography) in the guidelines-directed group, 42.3% (36 of the 85 patients) in the CMR group, and 43.5% in the MPS group (34 of the 78 patients).

CE-MARC 2 is only the last of a long series of studies investigating the role of noninvasive strategies in diagnosing IHD. Noninvasive tests are used for detection and/or assessment of the functional significance of epicardial stenosis. Similarly, the clinical pretest probability cited in major guidelines unconditionally refers to the probability of detecting CAD by coronary angiography. In line with previous studies, these findings confirm that, despite the adoption of progressively sophisticated tests and clinical prediction tools, there remains a significant divergence between the results from noninvasive strategies and those from invasive coronary angiography. Additionally, other studies have documented a high grade of variability among different noninvasive strategies. These findings are in line with the new paradigm for IHD, which considers obstructive CAD to be only one among many other determinants. Therefore, excluding or confirming obstructive CAD should not be the sole focus when evaluating a patient with suspected heart disease. In line with these considerations, there are two main issues with this approach. Firstly, only a minority of patients with chest pain will have obstructive CAD detected at coronary angiography, with as many as 55% to 75% of men and 75% to 90% of women with typical angina displaying no or mild CAD. Additionally, stable coronary plaques can be completely clinically silent. Secondly, contrary to expectations, revascularization by means of percutaneous coronary intervention performed in chronic IHD patients has a limited, if any, impact on prognosis. Indeed, whereas the risk of major cardiovascular events is known to increase with increasing CAD burden, this risk does not appear to be reduced by percutaneous coronary intervention.

Therefore, with the current attitude, we might be neglecting the patient subset with angina and no obstructive CAD and are probably overtreating those with obstructive CAD. Given also the low, but persistent, risk for adverse events and the increasing costs associated with invasive management, is it appropriate to continue investing major research efforts in developing the best strategy to identify and remove obstructive CAD? Instead of repeatedly praising the modest results of a single strategy, shouldn’t we take advantage of these tools and look carefully at the determinant factors behind the discordant results. This could be a first step toward a better understanding and treatment of patients with suspected chronic IHD.
Errare humanum est, perseverare autem diabolicum

REFERENCES


Angiogenesis
Angiogenesis is the physiological process by which new blood vessels are formed from preexisting blood vessels. Angiogenesis is a critical process in normal growth and development, wound healing, and repair, as well as in the formation of granulation tissue.

CD34+ cells
CD34+ cells are hematopoietic stem cells that express the protein CD34, which is also known as hematopoietic progenitor cell antigen CD34. CD34 is a protein identified by the cluster of differentiation nomenclature used to identify cell surface molecules, and it is a cell surface glycoprotein that has been shown to participate in cell-cell adhesion. Identification of CD34+ cells is often used as a marker for activated hematopoietic stem cells.

Framingham Heart Study
The Framingham Heart Study was initiated in 1948 as a joint effort between the National Heart Institute (now the National Heart Lung and Blood Institute) and Boston College and is now the longest running prospective cohort study in the United States. The objective of the study was to identify risk factors for the development of cardiovascular disease over time in participants who had not yet developed cardiovascular disease or suffered myocardial infarction or stroke. The first generation of participants was enrolled in Framingham, Massachusetts in 1948; a second generation, in 1971; and a third generation, in 2002 and 2003. The Framingham Heart Study has contributed to the understanding of overall and cardiovascular mortality in the setting of various pathologies, including obesity, diabetes, and metabolic syndrome.

Glycolysis
Glycolysis is the series of biochemical reactions occurring in the cytosolic compartment that converts a glucose molecule into two molecules of pyruvate. In the presence of oxygen (ie, the aerobic setting), pyruvate is transported into the mitochondria and undergoes oxidative decarboxylation, yielding acetyl coenzyme A. In the absence of oxygen (ie, the anaerobic setting), pyruvate is reduced to lactate by the enzyme lactate dehydrogenase, which generates the nicotinamide adenine dinucleotide (NAD+) required to maintain flux through glycolysis.

HbA1c
Glycated hemoglobin (HbA1c) forms from the non-enzymatic coupling of glucose to the major component of adult hemoglobin (ie, HbA αβ). Glucose, via a complex series of reactions, is coupled to specific valine residues of HbA β chains. HbA1c levels at a threshold of 6.5% can be used as a diagnostic test indicative of diabetes. HbA1c levels are reflective of average glycemic control over a period of 2 to 3 months before testing/analysis.

I$f$ current
The funny current ($I_f$), also referred to as a pacemaker current, is a hyperpolarization-activated inward current of mixed ionic nature (Na+, K+) that contributes to pacemaker activity in sinoatrial node cells (also atrioventricular node cells, and Purkinje fibers). The pore-forming subunits of the $I_f$ channel are formed by members of the hyperpolarization-activated cyclic nucleotide–gated gene family (HCN1-HCN4). As such, $I_f$ is responsive to changes in intracellular cyclic adenosine monophosphate (cAMP) levels in response to, for example, the activation of β adrenoceptors (increased cAMP) or M2 muscarinic receptors (decreased cAMP), and thus contributes to the basic physiological mechanisms mediating the effects of the autonomic nervous system on heart rate.

Microvascular dysfunction
Microvascular dysfunction (also known as small-vessel disease) occurs when damage arises in the walls and inner lining of the small coronary artery blood vessels that branch off from the larger coronary arteries (ie, left coronary artery). The damage in these smaller coronary artery blood vessels can produce spasms that decrease blood flow to the myocardium and thereby cause ischemia, and is more likely to develop in women.

Silent ischemia
Myocardial ischemia describes the situation where the heart/myocardium does not receive enough blood through the coronary circulation. The reduced blood flow and subsequent lack of oxygen delivery to the myocardium produces the sensation of chest pain, which is known as angina. If an individual does not experience the sensation of pain, it is referred to as “silent ischemia.” Individuals who have experienced previous heart attacks or are diabetic are at increased risk for developing silent ischemia.
**TNF-α**

Tumor necrosis factor-α (TNF-α) is a proinflammatory cytokine produced primarily by macrophages (also by other cells of the immune system, cardiac myocytes, adipocytes, fibroblasts, neurons). TNF-α is produced as a 216-amino-acid transmembrane protein arranged as homotrimers. The metalloproteinase, TNF-α converting enzyme (TACE/ADAM17) proteolytically cleaves transmembrane homotrimers, releasing soluble, 51-kDa TNF-α homotrimers. Both transmembrane and soluble TNF-α are biologically active, exerting effects via the activation of two receptor subtypes, TNFR1 (transmembrane, soluble TNF-α homotrimers) and TNFR2 (transmembrane TNF-α homotrimers).

**Variant angina**

Variant angina (also known as vasospastic angina) is a form of angina (sensation of chest pain) that occurs at rest in cycles. It is typically caused by a vasospasm, which is an arterial spasm that induces vasoconstriction of smooth muscle cells within the blood vessel wall, leading to myocardial ischemia.
In the next issue:
Cardiovascular diseases and diabetes: causes and cures

EDITORIAL
G. D. Lopaschuk

ORIGINAL ARTICLES
Diabetes: the cost of globalization?
P. M. Nilsson, L. Bennet

Better glycemic control and cardiovascular outcomes
G. D. Lopaschuk

Treating myocardial ischemia in diabetics: drugs, surgery, and stents
R. Belardinelli

Early detection of left ventricular dysfunction in diabetic patients
D. Y. Leung, M. Leung

Clinical benefits of targeting cardiac cells directly with trimetazidine in patients with coronary disease and diabetes
G. Fragasso, G. Anastasia, G. Monaca, G. Pinto

CASE REPORT
Managing chest pain in a diabetic patient
C. Scali

REFRESHER CORNER
Cardiac energy metabolism in diabetes
K. L. Ho, J. Ussher

HOT TOPICS
What cardiologists need to know about new drugs and new techniques to cure diabetes
J. E. Salles

GLOSSARY
G. D. Lopaschuk