“Chance favors only the prepared mind”
Pasteur

Metabolic agents in the contemporary treatment of angina

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Chronic ischemic heart disease (IHD) and stable angina are a major clinical problem worldwide. The prevalence of stable angina is estimated to be in the region of 20 000 to 50 000 per million in the general population.1,2 According to the REACH (REduction of Atherothrombosis for Continued Health) registry of more than 38 000 patients, 3 in every 20 patients with established coronary artery disease (CAD) has had a major event or been hospitalized within the previous year.3 Despite great advances in the management of CAD patients in recent times, symptoms are still common in many patients, sometimes even after revascularization. In the Heart and Soul Study, over a third (38%) of outpatients with stable CAD had angina, ischemia, or both.1 A substantial number of patients with typical angina do not have significant coronary atherosclerotic obstructions.4 Furthermore, the prevalence of coronary atherosclerotic obstruction in patients with or without typical angina is similar and is age-related in both sexes.

The treatment of stable CAD includes several potential strategies, including revascularization procedures (coronary artery bypass graft [CABG] or percutaneous coronary intervention [PCI]) and pharmacotherapy.5 One of the potential strategies for the treatment of CAD consists in targeting cardiac cells directly and in particular the energetic origin of ischemia with the use of a metabolic agent, such as trimetazidine, on top of β-blockers and other vasoactive agents.6

Myocardial ischemia is multifactorial and, above all, a deficiency in energy

Recent data clearly show that above and beyond coronary atherosclerotic obstruction, IHD is due to a large number of mechanisms, including coronary vasomotor, microcirculatory, endothelial, and platelet dysfunction and inflammation, among others.6 Because myocardial ischemia is multifactorial in nature, it should, above all, be defined as a deficiency in energy (in the form of ATP, adenosine triphosphate) at the cardiac cell level.7 Under conditions of energy deficit, drugs that act directly by increasing the energy supply in cardiac cells are of use, whatever the causal mechanism involved, and as such are essential for the optimal treatment of ischemia.

To protect myocardial cells from ischemia, energy supply needs to match energy demand. β-Blockers have a positive impact, reducing energy demand, while metabolic agents, such as trimetazidine, increase energy supply. That is why the use of an agent like trimetazidine fully complements β-blocker therapy.
Trimetazidine + β-blocker: an optimal combination for reducing angina

The TRIMPOL (TRIMetazidine in POLand) II study was one of the first studies to test the use of a metabolic agent on top of β-blockers in 426 patients with stable CAD. It was a randomized, multcenter, double-blind, placebo-controlled parallel group study. Patients with documented CAD and stable, effort-induced angina uncontrolled by metoprolol received either placebo or trimetazidine 20 mg three times daily in addition to metoprolol 50 mg twice daily. In this study, 12 weeks’ treatment with trimetazidine plus metoprolol significantly improved treadmill exercise test parameters and significantly reduced clinical symptoms compared with placebo plus metoprolol. This was achieved without any further hemodynamic changes in these patients. In addition to its antianginal efficacy, trimetazidine was well tolerated.

Michaelides et al performed a randomized, double-blind, controlled trial in angina patients who were symptomatic despite treatment with propranolol. The trial demonstrated that adding trimetazidine to treatment significantly decreased the mean number of angina attacks (–63%) twice as much as adding isosorbide dinitrate (–31%). This finding might be explained by the mode of action of trimetazidine, which provides a synergistic and complementary approach to hemodynamic agents, such as β-blockers. In a recent meta-analysis of almost 20 000 angina patients, trimetazidine was shown to be as effective as calcium channel blockers or nitrates at reducing ischemia and angina symptoms.

Nesukay demonstrated that directly adding trimetazidine to β-blockers in over 1400 patients with stable angina allowed for a quick reduction in angina symptoms, regardless of whether or not these patients who were on β-blockers were also on nitrates or calcium channel blockers.

Adding trimetazidine to β-blockers: evidence of improved prognosis in ischemic patients

In a recent heart failure registry, approximately 40% of chronic heart failure patients were found to have heart failure of ischemic origin. In a contemporary meta-analysis in nearly 1000 patients with heart failure, of mainly ischemic origin (93%), Gao et al showed that adding trimetazidine significantly reduced all-cause mortality as well as cardiovascular events and hospitalization for heart failure (P<0.01 versus placebo). In post–myocardial infarction patients with stable angina and heart failure, the use of modified-release trimetazidine was related to a significant reduction in major adverse cardiac events (cardiac death, nonfatal myocardial infarction, acute stroke, need for coronary revascularization, and hospitalization for unstable angina or heart failure) after 6 years of follow-up.

Adding trimetazidine to decrease ischemic reperfusion injury during revascularization and angina recurrence afterwards

Labrou et al have investigated whether the administration of trimetazidine before and after PCI minimizes procedure-induced myocardial damage and improves left ventricular function 1 and 3 months after PCI. Twenty-four hours after PCI, troponin I levels were >1 ng/mL in 26% of patients treated with trimetazidine versus 44% of patients in the control group. Forty-eight hours after revascularization, troponin levels remained elevated in 15% vs 32% of patients. About a fifth (22%) of patients in the trimetazidine group had creatine kinase MB (CK-MB) levels >5 ng/mL, 24 hours after PCI, compared with 40% in the control group.

The number of patients with an ejection fraction <50% was significantly reduced in the trimetazidine-treated group compared with the control group at 1 and 3 months after PCI: 11% versus 16% (P=0.046) after 1 month and 4% versus 16% (P=0.017) after 3 months. A significant improvement in regional wall motion versus placebo was noted after treatment with trimetazidine. The use of trimetazidine appeared to minimize myocardial reperfusion injury during PCI and improved global and regional wall motion 1 and 3 months after PCI, according to the authors.

The incidence of stent restenosis has risen, as increasing numbers of patients are treated with drug-eluting stents (DES). Chen et al evaluated whether long-term treatment with trimetazidine reduced the incidence of stent restenosis in 768 patients who underwent PCI with DES. The group on long-term trimetazidine treatment had a lower incidence of stent restenosis compared with the control group (4.2% vs 11.1%; P=0.001). At the 30-day follow-up, the trimetazidine patients exhibited a higher left ventricular ejection fraction than control patients (65.4±10.7% vs 63.1±10.4%; P=0.006). The incidence of major adverse cerebrovascular or cardiovascular events (MACCEs) was also lower in the trimetazidine group at 1-year follow-up (6.1% vs 10.8%; P=0.032). Treatment with trimetazidine was found to predict a reduction in stent restenosis (odds ratio [OR], 0.376; 95% CI, 0.196 to 0.721; P=0.003). The authors concluded that trimetazidine treatment effectively reduced the incidence of stent restenosis and MACCEs 1 year after DES implantation.
Xu et al. also appraised the effects of trimetazidine after DES implantation on recurrent angina pectoris and left ventricular structure in elderly patients with multivessel CAD and with diabetes mellitus and a left ventricular ejection fraction >50%. After 2 years, patients in the trimetazidine group were shown to have significant reductions in the incidence and severity of angina pectoris, compared with the control group, as well as a reduction in silent myocardial ischemia and increase in angina pectoris–free survival. Left ventricular function and structure in trimetazidine-treated patients were relatively stable after 2 years, but in control patients these parameters deteriorated. Adjunctive therapy with trimetazidine after DES implantation appears to have a beneficial effect in preventing recurrent angina pectoris as well as in improving left ventricular function and structure in elderly multivessel CAD patients with diabetes.

References

Conclusion
Chronic IHD is still a significant clinical burden in daily practice, and in stable angina β-blockers and revascularization procedures are extensively used treatments. Although the current pharmacological treatment of angina with vasoactive agents is effective, the addition to therapy of metabolic antianginal agents that act directly at the cardiac cell level could provide further treatment benefits, by targeting alternative mechanisms of ischemia. Moreover, use of these metabolic agents during and after revascularization procedures may also offer additional benefits, by decreasing ischemic repertusion injury and decreasing angina recurrence. Targeting the cardiac cell directly and addressing the energetic origin of ischemia with metabolic agents—such as trimetazidine—on top of treatment with vasoactive agents—such as β-blockers—seems a clinically pertinent strategy for managing IHD as effectively as possible.

Keywords: β-blocker; cardiac metabolism; myocardial ischemia; revascularization; stable angina; trimetazidine
La cardiopathie ischémique (CI) chronique et l’angor stable représentent un problème clinique majeur au niveau mondial. La prévalence de l’angor stable est estimée à environ 20 000 à 50 000 par million dans la population générale1,2. Selon le registre REACH (REduction of Atherothrombosis for Continued Health), qui comprend plus de 38 000 patients, 3 patients sur 20 ayant une maladie coronaire établie ont présenté un événement majeur ou ont été hospitalisés au cours de l’année précédente3.

Malgré d’importantes avancées dans la prise en charge des patients atteints de MC au cours des dernières années, de nombreux patients sont encore fréquemment symptomatiques, parfois même après une revascularisation. Dans l’étude Heart and Soul, plus d’un tiers des patients ambulatoires (38 %) présentant une MC stable avaient de l’angor, une ischémie ou les deux1. Un nombre important de patients présentant un angor typique n’ont pas d’obstruction athéroscléreuse coronaire significative4. En outre, la prévalence de l’obstruction athéroscléreuse coronaire chez les patients présentant ou non un angor typique est liée à l’âge et similaire et dans les deux sexes.

Le traitement de la MC stable repose sur plusieurs stratégies, notamment les procédures de revascularisation (pontage aorto-coronaire [PAC] ou intervention coronaire percutanée [ICP]) et la pharmacothérapie5. L’une des stratégies pouvant être utilisée dans le traitement de la MC consiste à cibler les cellules cardiaques directement, et en particulier l’origine énergétique de l’ischémie, en utilisant un agent métabolique, comme la trimétazidine, en complément des β-bloquants5.

L’ischémie myocardique est multifactorielle, mais c’est avant tout un déficit en énergie
Des données récentes montrent clairement qu’au-delà de l’obstruction coronaire par l’athérosclérose, la CI est provoquée par un grand nombre de mécanismes, notamment un dysfonctionnement vasomoteur coronaire, microcirculatoire, endothélial et plaquettaire et une inflammation6. L’ischémie myocardique étant de nature multifactorielle, elle devrait avant tout être considérée comme un déficit en énergie (sous forme d’ATP [adénosine triphosphate]) au niveau des cellules cardiaques7. En conditions de déficit énergétique, les médicaments qui agissent directement en augmentant l’énergie fournie aux cellules cardiaques sont utiles, quel que soit le mécanisme causal impliqué, et sont donc essentiels pour traiter l’ischémie de manière optimale.
Afin de protéger les cellules myocardiques de l’ischémie, l’apport en énergie doit répondre à la demande. Les β-bloquants ont un impact positif, en réduisant la demande énergétique, tandis que les agents métaboliques, comme la trimétazidine, augmentent l’apport en énergie. Un médicamente comme la trimétazidine complète donc parfaitement l’action des β-bloquants.

**Trimétazidine + β-bloquant : une association optimale pour réduire l’angor**

L’étude TRIMPOL II (TRIMetazidine in POLand) a été l’une des premières à tester l’utilisation d’un agent métabolique en complément des β-bloquants chez 426 patients atteints de MC stable. Dans cette étude randomisée, multicentrique, en double aveugle, contrôlée par placebo et en groupes parallèles, les patients atteints de MC documentée et d’angor stable induit par l’effort, non contrôlé par le métoprolol, ont reçu soit un placebo, soit 20 mg de trimétazidine trois fois par jour, en complément de deux doses quotidiennes de 50 mg de métoprolol. Un traitement de 12 semaines avec l’association trimétazidine plus métoprolol a permis d’améliorer de manière significative les paramètres de l’effort sur tapis roulant et a réduit significativement les symptômes cliniques par rapport à l’association placebo plus métoprolol. Ces résultats ont été obtenus sans changements hémodynamiques supplémentaires chez ces patients. Outre son efficacité antiangoureuse, la trimétazidine a été bien tolérée.

Michaelides et coll. ont réalisé une étude contrôlée, randomisée et en double aveugle chez des patients atteints d’angor, encore symptomatiques malgré un traitement par le propranolol. Cette étude a démontré que l’ajout de trimétazidine permet de diminuer significativement le nombre moyen de crises d’angor de manière deux fois plus efficace que l’ajout du dinitrate d’isosorbide (-63 % vs -31 %). Ce résultat pourrait permettre de diminuer significativement le nombre moyen de crises d’angor de manière deux fois plus efficace que l’ajout du dinitrate d’isosorbide (-63 % vs -31 %). Ce résultat pourrait permettre de diminuer significativement le nombre moyen de crises d’angor de manière deux fois plus efficace que l’ajout du dinitrate d’isosorbide (-63 % vs -31 %). Ce résultat pourrait permettre de diminuer significativement le nombre moyen de crises d’angor de manière deux fois plus efficace que l’ajout du dinitrate d’isosorbide (-63 % vs -31 %). Ce résultat pourrait permettre de diminuer significativement le nombre moyen de crises d’angor de manière deux fois plus efficace que l’ajout du dinitrate d’isosorbide (-63 % vs -31 %). Ce résultat pourrait permettre de diminuer significativement le nombre moyen de crises d’angor de manière deux fois plus efficace que l’ajout du dinitrate d’isosorbide (-63 % vs -31 %). Ce résultat pourrait permettre de diminuer significativement le nombre moyen de crises d’angor de manière deux fois plus efficace que l’ajout du dinitrate d’isosorbide (-63 % vs -31 %).

**Ajout de la trimétazidine aux β-bloquants : amélioration du pronostic chez les patients ischémiques**

L’analyse d’un registre récent de patients souffrant d’insuffisance cardiaque a montré qu’environ 40 % des patients insuffisants cardiaques chroniques présentaient une pathologie d’origine ischémique. Dans une méta-analyse contemporaine menée chez près de 1 000 patients atteints d’insuffisance cardiaque, principalement d’origine ischémique (93 %), Gao et coll. ont montré que l’addition de trimétazidine réduisait significativement la mortalité de toute cause, ainsi que les événements cardio-vasculaires et l’hospitalisation pour insuffisance cardiaque (p < 0,01 vs placebo). Chez les patients en post-infarctus du myocarde présentant un angiographie stable et une insuffisance cardiaque, un suivi de six ans a montré que l’utilisation de trimétazidine à libération modifiée était liée à une réduction significative des événements cardio-vasculaires majeurs (mortalité cardiaque, infarctus du myocarde non fatal, accident vasculaire cérébral aigu, nécessité d’une revascularisation coronaire et hospitalisation pour angor instable ou insuffisance cardiaque). Un traitement de 12 semaines avec l’association trimétazidine plus métoprolol a permis d’améliorer de manière significative les paramètres des épreuves d’effort sur tapis roulant et a réduit significativement les symptômes cliniques par rapport à l’association placebo plus métoprolol. Ces résultats ont été obtenus sans changements hémodynamiques supplémentaires chez ces patients. Outre son efficacité antiangoureuse, la trimétazidine a été bien tolérée.

**Ajout de la trimétazidine pour diminuer les lésions de reperfusion ischémique au cours de la revascularisation et les récidives d’angor par la suite**

Labrou et coll. ont cherché à déterminer si l’administration de trimétazidine avant et après une ICP diminue les lésions myocardiques induites par la procédure et améliore la fonction ventriculaire gauche 1 et 3 mois après une ICP. Vingt-quatre heures après l’ICP, 26 % des patients traités par trimétazidine avaient un taux de troponine I > 1 ng/ml, contre 44 % dans le groupe témoin. Quarante-huit heures après la revascularisation, les taux de troponine restaient élevés chez 15 % du groupe trimétazidine, contre 32 % dans le groupe témoin. Environ un cinquième des patients (22 %) du groupe trimétazidine présentaient des taux de créatine kinase MB (CK-MB) > 5 ng/ml, 24 heures après l’ICP, contre 40 % dans le groupe témoin. Le nombre de patients montrant une fraction d’éjection < 50 % a diminué de manière significative dans le groupe traité par la trimétazidine, par rapport au groupe témoin : 11 % vs 16 % (p = 0,046) 1 mois après l’ICP, et 4 % vs 16 % (p = 0,017) 3 mois après l’ICP. Une amélioration significative de la mobilité pariétale locale a été observée après le traitement par la trimétazidine par rapport au placebo. D’après les auteurs, l’utilisation de la trimétazidine semble minimiser les lésions myocardiques de reperfusion au cours de l’ICP et améliorer la mobilité pariétale globale et régionale 1 et 3 mois après l’ICP.
Le nombre de patients traités par stents actifs (endoprothèses à libération de principe actif) ayant augmenté, l’incidence des resténoses intra-stent est en progression. Chen et coll. ont évalué dans quelle mesure un traitement à long terme par la trimétazidine pouvait réduire l’incidence des resténoses intra-stent chez 788 patients ayant bénéficié d’une ICP avec un stent actif. L’incidence des resténoses intra-stent était inférieure dans le groupe ayant reçu un traitement à long terme par la trimétazidine par rapport au groupe témoin (4,2 % vs 11,1 % ; p = 0,001). Après 30 jours de suivi, la fraction d’éjection ventriculaire gauche des patients sous trimétazidine était supérieure à celle des patients du groupe témoin (65,4 ± 10,7 % vs 63,1 ± 10,4 % ; p = 0,006). L’incidence des événements vasculaires cérébraux ou cardio-vasculaires majeurs (major adverse cerebrovascular or cardiovascular events, MACCE) était également inférieure dans le groupe recevant la trimétazidine lors du suivi à un an (6,1 % vs 10,8 % ; p = 0,032). Le traitement par la trimétazidine s’est avéré être un facteur prédictif de la réduction des resténoses intra-stent (odds ratio, OR : 0,376 ; intervalle de confiance IC à 95 % : 0,196 à 0,721 ; p = 0,003). Les auteurs ont conclu qu’un traitement par la trimétazidine réduisait de manière efficace l’incidence des resténoses intra-stent et des MACCE un an après la mise en place d’un stent actif.

Xu et coll. ont également évalué les effets de la trimétazidine après la mise en place d’un stent actif sur la récidive de l’angor et sur la structure du ventricule gauche chez des patients âgés atteints de MC pluritronculaire et d’un diabète, et présentant une fraction d’éjection ventriculaire gauche > 50 %. Après deux ans, des réductions significatives de l’incidence et de la sévérité de l’angor, une diminution de l’ischémie myocardique silencieuse et une augmentation de la survie sans angor ont été observées chez les patients du groupe trimétazidine par rapport au groupe témoin. La fonction et la structure du ventricule gauche chez les patients traités par la trimétazidine sont restées relativement stables après deux ans, alors que chez les patients témoins ces paramètres se sont détériorés. Un traitement complémentaire par la trimétazidine après la mise en place d’un stent actif semble exercer un effet bénéfique sur la prévention des récidives d’angor, et sur l’amélioration de la fonction et de la structure du ventricule gauche chez des patients âgés diabétiques présentant une MC pluritronculaire.

**Conclusion**

Chronic ischemic heart disease: an energy imbalance

by G. Guarini and M. Marzilli, Italy

Alterations in cardiac metabolism have recently been implicated in the pathophysiology of ischemic heart disease. In normal conditions, the heart derives most of its energy from β-oxidation of free fatty acids. However, the healthy heart can easily switch from one substrate to another according to substrate availability, nutritional status, and exercise level. Paradoxically, during prolonged and severe ischemia, the myocardium continues to derive most of its energy (up to 90%) from β-oxidation. A greater amount of oxygen is required to completely oxidize a fatty acid with a carbon-chain length equivalent to that of glucose. Fatty acid oxidation is thought to be detrimental in that, while requiring more oxygen, it produces less adenosine triphosphate (ATP) and more reactive oxygen species, thus further reducing mitochondrial respiratory efficiency. Aside from metabolic alterations, the process of producing and utilizing energy is very complex and includes multiple steps from uptake of metabolites by cardiac myocytes, oxidative phosphorylation in the mitochondria, and transport of ATP to intracellular components. Therefore, impairment in any one of these steps can have a tremendous impact on cell homeostasis. In addition to acute and chronic changes in cardiac metabolism, mitochondrial dysfunction has been implicated in promoting myocardial ischemia and myocardial damage during the reperfusion phase of an ischemic event, thereby further reducing the heart’s ability to synthesize and utilize ATP.

Despite a global reduction in cardiovascular mortality owing to improved therapy and well-designed educational programs, ischemic heart disease (IHD) remains the most important cause of death in Western countries. In the United States, in the 10-year period from 2003 to 2013, death rates attributable to cardiovascular disease (CVD) declined by 28.8%, while the actual number of CVD deaths per year declined by 11.7%. Even so, CVD still accounted for 30.8% of all deaths (i.e., 1 out of every 3 deaths) in the United States in 2013. That same time period witnessed a decline in the prevalence of angina pectoris: between 2009 and 2012, there was an average of 3.4 million people aged 40 years or over in the United States with angina each year compared with 4 million between 1988 and 1994.¹ In Europe, as in the United States, the prevalence of angina increases with age, with prevalence ranging from 2%-5% in men aged 45-54 years to 11%-20% in men aged over 60; in women, from 0.5%-1% to 10%-14%, respectively.²
Myocardial ischemia is often due to coronary atherosclerotic disease, which limits coronary blood flow, causing an imbalance between available blood supply and the heart's metabolic demands. Anti-ischemic therapy is based on this concept and focuses on alleviating the problem by removal of the coronary obstructions by mechanical means, and/or modulating cardiac work and coronary blood flow through pharmacological agents. Although such therapeutic strategies aim to restore an adequate supply/demand balance, to improve symptoms, and to prolong survival, available evidence indicates that this goal is not always reached. Indeed, a number of trials report persistent angina in over 30% of patients despite optimal medical therapy and despite “successful” coronary revascularization, both in patients treated by percutaneous coronary intervention and those treated by coronary artery bypass graft (CABG) surgery.3-5

The unexpected prevalence of angina despite optimal medical therapy plus successful revascularization strongly challenges the current approach to treating IHD. Up to this point, cardiologists have focused on the vascular inability to supply myocytes with sufficient oxygen and nutrients. Only recently has the scientific community considered additional mechanisms that may contribute to myocardial ischemia. Just as there may be multiple paths to a dysfunctional car engine, there may be multiple paths to myocardial ischemia. In this analogy, an inadequate blood supply for the heart would be like a shortage of gasoline for a car; an impaired cellular uptake of nutrients would be like an altered transmission of gasoline to the car engine; mitochondrial dysfunction, like an engine's inability to transform chemical energy into mechanical energy; and an inability to transfer adenosine triphosphate (ATP) to the cellular contractile machinery, like an inability of the engine's receiving system to generate external work. Indeed, free fatty acids (FFAs) and glucose that are taken up by the cells need to be transformed into intermediary components (acetyl coenzyme A [CoA]) by β-oxidation and glycolysis so that they can enter the Krebs cycle and produce carbon dioxide (CO2) and nicotinamide adenine dinucleotide (NADH), a key substrate of oxidative phosphorylation. Respiratory-chain complexes I through IV transfer electrons from NADH to oxygen, creating a proton electrochemical gradient (ΔH+) across the inner mitochondrial membrane. This gradient is used by ATP synthase to phosphorylate adenosine diphosphate (ADP), thereby producing the high-energy phosphate compound ATP, the direct source of energy for all energy-consuming reactions in the heart. Once generated in the mitochondria, ATP is transferred by the creatine kinase energy shuttle to myofibrils and to sarclemmal and sarcoplasmic reticulum ion pumps. On the basis of these considerations and an overwhelming body of evidence, factors other than epicardial stenosis, such as mitochondrial dysfunction and metabolic derangement, have been recognized as pathological mechanisms for persistent ischemia.6-7

Due to the complex pathophysiology of IHD, some challenging questions about treatment arise. How should we deal with persistent angina in patients that have already been revascularized? Which drugs can be used to treat IHD in patients free of coronary stenosis? Indeed, most available antianginal drugs were developed to counteract the effects of a flow-limiting stenosis, and their efficacy has been attributed to their ability to either increase coronary blood flow or to decrease myocardial oxygen demand. None of these agents were tested after the removal of the flow-limiting stenosis. The incomplete success with current treatment has fostered a large interest in therapeutic strategies that target the “alternative pathological mechanisms,” i.e., metabolic modulation. Indeed, there is evidence that metabolic modulation therapy may play a key role in the acute phase of ischemic events, where it would affect results of acute interventions on the subsequent development of heart failure (HF)—stunned and hibernated myocardium—as well as for those who experience chronic stable angina.8 Our improved understanding of metabolic changes that occur during ischemic events and after reperfusion is now being translated into new therapeutic opportunities.

**Ischemic heart disease: an energy crisis**

Significant progress has been made in recent years in understanding the role of cardiac energy metabolism in the pathogenesis of myocardial ischemia. As a natural consequence, a better understanding of the metabolic derangements associated with IHD is translating into new therapeutic strategies.

Under normal conditions, the healthy heart derives approximately two-thirds of its energy (in the form of ATP) from the FFA pathway; glucose oxidation and pyruvate are the other
source for the remainder of the energy produced. The healthy heart switches easily from one substrate to another as needed, according to substrate availability, nutritional status, and exercise level. The myocardium responds to mild-to-moderate cardiac ischemia by increasing uptake of glucose so that it can produce the ATP necessary to maintain ionic gradients and calcium (Ca<sup>2+</sup>) homeostasis. Paradoxically and to detrimental effect, the myocardium continues to rely on β-oxidation for production of most of its energy (90%) during prolonged and severe ischemia, despite the elevated lactate production that occurs under these conditions. Furthermore, due to the Randle phenomenon—a competitive interaction between fatty acid (FA) oxidation and glucose oxidation—high rates of FA oxidation inhibit glucose oxidation, already low, even further. Although the complete oxidation of FAs produces more ATP per molecule of CO<sub>2</sub> than that produced from the complete oxidation of glucose, more oxygen is used to completely oxidize a FA of equivalent carbon-chain length. Therefore, glucose oxidation, which produces roughly 15% more ATP for a given amount of oxygen used, is considered more "oxygen sparing" than FA oxidation. During ischemia, FA oxidation can become detrimental, because it uses more oxygen and produces less ATP and more reactive oxygen species (ROS), and so further depresses mitochondrial respiratory efficiency. FFAs activate their own uptake and oxidation and they antagonize the uptake of glucose, lactate, and pyruvate, in part through direct inhibition of pyruvate dehydrogenase. The effects of FFAs on the mitochondria include uncoupling of cellular respiration, resulting in decreased ATP production and oxygen wasting. Thus, excessive levels of FFAs in the blood lead to lactate and proton accumulation, lowered cellular pH, and disrupted cellular function, as well as impaired Ca<sup>2+</sup> handling, oxidative stress, reduced activity of the glucose transporter GLUT-4, and apoptosis of myocytes. Such metabolic changes disrupt cell homeostasis and alter membrane structure, and they ultimately lead to cell death.

Interestingly, derangements in myocardial energy metabolism are associated with heart failure (HF) as well: such altered metabolism is the final common pathway of several cardiac disorders, such as IHD, cardiomyopathies, hypertension, and diabetes-induced HF. Recent data suggest that HF may itself promote metabolic changes, such as insulin resistance, in part through neurohumoral activation, generating a vicious cycle in which metabolic abnormalities further aggravate and precipitate HF. The associations between altered energy metabolism, insulin resistance, and HF may be explained by the following compatible processes: (i) activation of the neurohumoral system, including the sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone system (RAAS); (ii) inflammation, indicated by increased levels of tumor necrosis factor α (TNF-α) and its soluble receptors; (iii) alterations in skeletal muscle function and mass as a result of reduced physical activity; (iv) endothelial dysfunction; (v) increased adipocytokines, such as adiponectin and leptin; and (vi) pharmacological exacerbation of insulin resistance (eg, by diuretics). Of these, neurohumoral activation has been the most studied and is probably the strongest contributor to altered metabolism in HF. Neurohumoral homeostasis is activated in response to a long-term depression in cardiac output—characterized by persistent activation of the SNS and the interlinked RAAS—resulting in increased catecholamine secretion. At the same time, catecholamines reuptake in the heart is decreased. Increased levels of catecholamines are directly detrimental to the heart, causing substantial enzyme loss as an index of diffuse myocardial damage, and much oxygen wastage even in the absence of FFAs in the perfusate. Furthermore, the catecholamine norepinephrine promotes both coronary vasoconstriction and increased plasma FFA levels, further exacerbating oxygen wastage. Therefore, addressing the abnormal cardiac metabolism in IHD patients may also improve patient prognosis by halting the progression to HF.

Ischemic heart disease: a mitochondrial issue

Aside from their key role in energy production and metabolic modulation, mitochondria are essential to cardiomyocyte survival during ischemia and reperfusion. They are implicated in ATP synthesis, maintenance of Ca<sup>2+</sup> homeostasis, cell survival, and cardioprotection, all of which are regulated by the proton gradient across the mitochondrial membrane. Under aerobic physiologic conditions, mitochondria are not involved in the beat-to-beat regulation of cytosolic Ca<sup>2+</sup> levels, though a small flux of Ca<sup>2+</sup> into the mitochondrial matrix has been observed. Small increases in mitochondrial Ca<sup>2+</sup> concentration stimulate the Krebs cycle and the NADH redox potential. This fine regulation of mitochondrial Ca<sup>2+</sup> is important to enhance oxidative phosphorylation and ATP synthesis. However, under pathological conditions, mitochondria can take up too much Ca<sup>2+</sup>, activating a series of steps that trigger a vicious cycle that ultimately leads to irreversible cell damage. During ischemia, intracellular Ca<sup>2+</sup> homeostasis is deranged; however, mitochondria can still buffer cytosolic Ca<sup>2+</sup>, suggesting that they do not lose their ability to pump Ca<sup>2+</sup>. Mitochondria isolated after prolonged periods of ischemia are still able to use oxygen for ATP phosphorylation. Conversely, mitochondria isolated after reperfusion are structurally altered; their membrane pores are open; they contain large amounts of Ca<sup>2+</sup>; they produce large amounts of oxygen free radicals, and the oxidative phosphorylation system is irreversibly damaged. In addition, ischemia followed by reperfusion induces irreversible deletions in several parts of the mitochondrial genome, impairing ATP production, which is ultimately responsible for cardiomyocyte death (ischemia-reperfusion injury).

Notably, strategies that confer cardioprotection from myocardial ischemia-reperfusion injury involve the activation of the reperfusion injury salvage kinase (RISK) and survival activating factor enhancement (SAFE) pathways and the inhibition of mitochondrial permeability transition pore (MPTP) opening. The MPTP is a nonselective channel located on the inner mi-
These findings are supported by a link between key glycolytic and angina symptoms in patients with IHD with long-term use. Not only to provide cardioprotection in the acute phase of an ischemic event, but also to ameliorate cardiac metabolism and angina symptoms in patients with IHD with long-term use. These findings are supported by a link between key glycolytic enzymes and the activity of two membrane-bound pumps considered to be survival promoting—the sodium-potassium ATPase and the Ca²⁺-uptake pump of the sarcoplasmic reticulum. Indeed, ischemia-induced derangement of cardiac metabolism can be minimized through treatment with metabolic modulators that decrease FA oxidation and increase utilization of glucose and lactate as energy substrates. The greatest progress in the use of metabolic therapy occurred with the advent of the direct inhibitors of myocardial FA oxidation, specifically trimetazidine, discussed next in further detail. 

Trimetazidine
Trimetazidine was the first and, for many years, the only registered drug in its class. It is available in over 80 countries worldwide. It has an established antianginal efficacy, known even before the discovery of how the drug acts, which is via partial inhibition of myocardial FA oxidation. Initial preclinical studies in animal models of myocardial ischemia and reperfusion demonstrated a cytoprotective effect for this drug. It has been shown by Kantor et al to specifically inhibit the long-chain activity of the enzyme 3-ketoacyl CoA thiolase (EC 2.3.1.16) (3-KAT), the enzyme that catalyzes the last step in FA β-oxidation, using long-chain 3-ketoacyl-CoA as a substrate to generate acetyl-CoA. Trimetazidine's inhibition of 3-KAT reduces the NADH/NAD+ and acetyl-CoA/free CoA ratios in the mitochondrial matrix, in effect removing the inhibition on pyruvate dehydrogenase and thus increasing the rate of glucose oxidation. Indeed, in the working rat heart, although only modestly reducing the rate of FA oxidation, trimetazidine significantly increases the rate of glucose oxidation. In the TACT study (Trimetazidine in Angina Combination Therapy), in that study, exercise stress test parameters and angina symptoms were significantly improved with the addition of trimetazidine to therapy including β-blockers or long-acting nitrates, compared with addition of placebo. Similar results were observed in the VASCO-Angina study. This randomized, double-blind, placebo-controlled trial, assessed antianginal efficacy on exercise test parameters and safety of both a standard dosage (70 mg/day) and a high dosage (140 mg/day) of modified-release trimetazidine in symptomatic and asymptomatic patients with chronic stable angina who were receiving background β-blocker therapy with atenolol (50 mg/day). That study confirmed the efficacy and tolerability of both trimetazidine dosages in improving effort-induced myocardial ischemia and functional capacity in such patients. Furthermore, evidence from other studies suggest trimetazidine may improve clinical manifestation in patients with stable IHD. Indeed, with long-term administration of trimetazidine, the following have been observed: a lower average number of weekly attacks, a low-

**Innovative approaches to manage myocardial ischemia: mitochondria and cardiac energy metabolism modulators**

On the basis of this biochemical background, the pharmacological manipulation of mitochondria to optimize cardiac energy metabolism makes for an attractive therapeutic option. Such an approach is largely based on the promotion of cardiac glucose oxidation along with the suppression of β-oxidation, leading to an improvement in cardiac function and protection against ischemia-reperfusion injury, as well as attenuation of progression to congestive HF (CHF). Owing to the Randle phenomenon, carbohydrate metabolism may be indirectly decreased by a decreasing rate of FA oxidation. Such a decrease in FA oxidation may be achieved in different ways. One of these involves decreasing the availability of FAs as an energy substrate; this can be achieved through treatment with glucose, insulin, and potassium (GIK therapy), which decreases the circulating levels of FFAs and/or their uptake by cardiac myocytes, or through suppression of carnitine palmitoyl transferase (CPT) I or II to inhibit FA uptake by the mitochondria. Another way to decrease FA oxidation is by direct inhibition of the enzymes involved. Of note, drugs that can manipulate FFA oxidation (eg, trimetazidine) have been shown not only to provide cardioprotection in the acute phase of an ischemic event, but also to ameliorate cardiac metabolism and angina symptoms in patients with IHD with long-term use. These findings are supported by a link between key glycolytic
er mean weekly consumption of short-acting nitrates, improvement in quality of life, lessened severity of main clinical manifestations of chronic HF, and improved (lowered) functional class. 26-29 Moreover, as trimetazidine has been demonstrated to have similar efficacy in men and women, this metabolic myocardial cytoprotector can be recommended for patients with IHD irrespective of sex. 30,31 Trimetazidine has also been used for cardioprotection in patients undergoing coronary bypass surgery and percutaneous coronary intervention. 26,31 Consistent with IHD and HF being considered energetic disorders, trimetazidine was effective in reducing mortality and event-free survival in patients with chronic HF in an international, multicenter, retrospective cohort study. The addition of trimetazidine to optimal medical therapy improved long-term survival in these patients. 31 That retrospective analysis further confirmed the results of previous small studies in patients with chronic HF that had shown that trimetazidine improves left ventricular function, exercise capacity, and New York Heart Association functional class compared with placebo. Furthermore, the addition of trimetazidine to exercise training resulted in greater improvements in functional capacity, left ventricular ejection fraction, and endothelium-dependent dilation in patients with chronic HF. 34

Conclusions: ischemic heart disease, an energetic disorder

Historically, IHD has been considered a vascular disease, where coronary atherosclerosis causes an imbalance between blood supply and demand. However, recent evidence suggests that cardiac metabolic derangement and the inability of mitochondria to efficiently produce energy are able to induce energy starvation similar to that produced by coronary blood flow blockage. In other words, it is conceivable that cardiac metabolic derangements and/or mitochondrial dysfunction can directly put the myocardium under ischemic conditions, independently of oxygen and nutrient availability. Accordingly, in an experimental model (Zucker obese fatty rat), repairing mitochondrial DNA damage improved mitochondrial function, restored vascular and myocyte properties, and reduced the consequences of oxidative stress. 35 Similarly, in Zucker lean rats in which mitochondrial dysfunction was selectively induced through mitochondrial DNA damage, areas of myocardial ischemia, endothelial dysfunction, and depressed contractile function under cardiac stress were observed in the absence of coronary atherosclerosis. 36 These observations support the hypothesis that myocardial ischemia should be considered an energetic disorder.

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Keywords: cardiac metabolism; ischemic heart disease; metabolic agent; mitochondrial dysfunction

LA MALADIE CORONAIRE CHRONIQUE : UN DÉSÉQUILIBRE ÉNERGÉTIQUE

Récemment, des altérations du métabolisme cardiaque ont été impliquées dans la physiopathologie de la maladie coronaire. En conditions normales, la plus grande partie de l’énergie cardiaque provient de la β-oxydation des acides gras libres. Cependant, le cœur sain peut facilement passer d’un substrat à un autre selon la disponibilité du substrat, l’état nutritionnel et le niveau d’effort. Paradoxalement, au cours d’une ischémie prolongée et sévère, le myocarde continue de tirer la plupart de son énergie (jusqu’à 90 %) de la β-oxydation. Il faut une plus grande quantité d’oxygène pour oxyder complètement un acide gras avec une chaîne de carbone dont la longueur est équivalente à celle du glucose. L’oxydation des acides gras est considérée comme préjudiciable car elle produit moins d’ATP et plus de dérivés réactifs de l’oxygène, tout en nécessitant plus d’oxygène, ce qui réduit donc encore l’efficacité de la chaîne respiratoire mitochondriale. Hormis les changements métaboliques, le processus de production et d’utilisation de l’énergie est très complexe et comprend de nombreuses étapes : l’absorption des métabolites par les myocytes cardiaques, la phosphorylation oxydative dans les mitochondries et le transport de l’ATP vers les différents compartiments intracellulaires. C’est ainsi qu’une détérioration de l’une de ces étapes peut avoir un impact néfaste sur l’hémodynamique cellulaire. En plus des changements aigus et chroniques du métabolisme cardiaque, il a été montré que la dysfonction mitochondriale favorise l’ischémie myocardique et les troubles myocardiques pendant la phase de reperfusion d’un événement ischémique, ce qui réduit alors encore un peu plus l’aptitude du cœur à synthétiser et à utiliser l’ATP.
Mitochondria as a therapeutic target in ischemia

by D. J. Hausenloy, United Kingdom

Ischemic heart disease is the leading cause of death and disability worldwide. As such, novel therapeutic targets are urgently required to protect the heart against the detrimental effects of acute ischemia/reperfusion injury in order to preserve cardiac function and improve clinical outcomes in patients with ischemic heart disease. In this regard, mitochondria, which are the powerhouses of the cell and which make up one-third of the volume of a cardiomyocyte, are an important target for cardioprotection. Elucidation of the signaling pathways underlying the endogenous cardioprotective phenomenon of ischemic conditioning, in which the heart can be protected by brief nonlethal episodes of ischemia and reperfusion, has identified mitochondria to be the end-effector in many of the signal transduction pathways. In this article, we review the role of mitochondria as targets for protecting the heart against acute ischemia/reperfusion injury, the therapeutic application of which should help improve clinical outcomes in patients with ischemic heart disease.

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Metabolic and biochemical consequences of acute ischemia/reperfusion

An acute coronary artery occlusion results in a critical reduction in coronary blood flow and deprivation of oxygen and nutrients to the affected area of myocardium, and it impairs the clearance of waste metabolites, subjecting cardiomyocytes to the abrupt metabolic and biochemical changes associated with acute myocardial ischemia. If blood flow is restored to the affected area by the removal of the coronary artery occlusion, the ischemic myocytes are then exposed to the further metabolic and biochemical changes associated with the reperfusion process. The combined injury sustained by the myocardium during these processes is termed acute myocardial IRI, and the sequential metabolic and biochemical perturbations that oc-
Cur during this process are reviewed below and presented in Figure 1. Deprivation of oxygen during acute myocardial ischemia impairs oxidative phosphorylation by reducing electron flow through the mitochondrial electron transport chain, leading to an accumulation of NADH and FADH and cessation of adenosine triphosphate (ATP) production. The mitochondrial membrane potential collapses as it is no longer maintained by the electrochemical gradient across the inner mitochondrial membrane. Intracellular creatine phosphate is depleted with a concomitant rise in intracellular inorganic phosphate (Pi), resulting in mitochondria accumulating Pi. Residual reserves of ATP are hydrolyzed by F$_2$F$_{-1}$-ATPase in an attempt to restore the mitochondrial membrane potential, resulting in catalytic metabolites such as hypoxanthine, which are oxidized to release free radicals. The activity of the adenine nucleotide translocase is reduced, impairing oxidative phosphorylation further still.

The reduced availability of ATP and oxygen drives anaerobic glycolysis, which results in lactic acid accumulation, leading to intracellular acidification. The fall in pH activates the sodium (Na+)/hydrogen (H+) exchanger in an effort to remove cytosolic protons, which causes the entry of Na$. The Na$'/potassium (K$-)ATPase, which normally removes excess Na$, is inhibited because of the reduced availability of ATP and the increase in intracellular Pi. This results in a rise in intracellular Na$, which triggers the Na$'/calcium (Ca$2+) exchanger to function in reverse in order to remove cytosolic Na$. However, this occurs at the expense of an increase in intracellular Ca$2+. The rise in cytosolic Ca$2+ results in the mitochondrial accumulation of Ca$2+ via the mitochondrial Na'/Ca$2+ exchanger. The onset of rigor contracture coincides with the depletion of ATP, and is followed by cellular Ca$2+ overload.

Reperfusion of acutely ischemic myocardium has several important consequences: (i) re-energization of the cardiomyocyte, causing repolarization of the mitochondrial membrane potential; (ii) reoxygenation of a reduced mitochondrial respiratory chain, resulting in the production of reactive oxygen species (ROS) and oxidation of NADH/FADH; (iii) a drop in intracellular Ca$2+, but a further influx of Ca$2+ into mitochondria via the Ca$2+-uniporter driven by the restored mitochondrial membrane potential; and (iv) the wash-out of lactic acid, which in combination with the reactivation of the Na$'/H$ exchange acts to restore a neutral pH. Many of the biochemical and metabolic changes that take place during the first few minutes of reperfusion can mediate cardiomyocyte death by inducing the opening of the mitochondrial permeability transition pore (MPTP) opening and cardiomyocyte hypercontracture.

![Figure 1](image)

**Figure 1.** The metabolic and biochemical changes that occur during acute myocardial ischemia and reperfusion.

During acute myocardial ischemia, there is an increase in intracellular calcium (Ca$^{2+}$), inorganic phosphate (Pi), sodium (Na$^+$), reactive oxygen species (ROS), NADH, and hydrogen (H$^+$), a fall in adenosine triphosphate (ATP) levels, and collapse of the mitochondrial membrane potential ($\Delta$$\psi$). At reperfusion, there is repolarization of the $\Delta$mem and restoration of mitochondrial ATP production; a further increase in Ca$^{2+}$, Pi, and ROS; oxidation of NADH; and restoration of neutral pH—factors that mediate cell death by inducing mitochondrial permeability transition pore (MPTP) opening and cardiomyocyte hypercontracture.
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**Figure 2.** Mitochondrial targets for cardioprotection.

The diagram provides a simplified scheme of some of the potential mitochondrial targets for cardioprotection, many of which have been elucidated from studies investigating the signaling pathways underlying ischemic conditioning. These signal transduction pathways include the RISK (involving PI3K-Akt and MEK1/2-Erk1/2), SAFE (involving JAK-STAT), and NO-cGMP pathways, all of which terminate at the mitochondria and, particularly, the mitochondrial permeability transition pore (MPTP). These reperfusion salvage pathways have been shown to activate downstream mediators, such as eNOS, GSK3β, HKII, PKCε, and KCl, which then mediate the inhibitory effect on MPTP opening. The modulation of mitochondrial energetics by actions on the electron transport chain and adenosine triphosphate production can also indirectly prevent MPTP opening in response to acute ischemia/reperfusion injury (IRI).

Cyclosporin A protects against acute IRI by inhibiting MPTP opening via inhibition of CypD. TRO40303 is believed to protect the heart by inhibiting MPTP opening via attenuation of reactive oxygen species (ROS) production in response to acute IRI. MTP-131 protects the heart against acute IRI by improving mitochondrial energetics via targeting of cardiac Ca2+ in the inner mitochondrial membrane. Trimeprazine protects the heart against acute IRI by inhibiting fatty acid oxidation, thereby promoting glucose oxidation, the result of which is improved mitochondrial energetics. Nabradine protects the heart against acute IRI by lowering the heart rate and through pleotropic effects, which include attenuation of ROS production and inhibition of MPTP opening.

**Abbreviations:** cGMP, cyclic guanosine monophosphate; Cardio, cardioprotection; CypD, cyclophilin D; eNOS, endothelial nitric oxide synthase; Erk1/2, extracellular signal–regulated kinase 1/2; ETC, electron transport chain; GSK3β, glycogen synthase kinase 3β; HKII, Hexokinase II; IRI, ischemia/reperfusion injury; JAK, Janus kinase; KATP, mitochondrial ATP-dependent potassium channel; MEK1/2, mitogen-activated protein kinase (MAP)/extracellular signal–regulated kinase (ERK)1/2; MPTP, mitochondrial permeability transition pore; NO, nitric oxide; PI3K, phosphatidylinositol 3-kinase; PKCε, protein kinase C epsilon; PKG, protein kinase G; ROS, reactive oxygen species; SAFE, survival activating factor enhancement; STAT, signal transducer and activator of transcription; RISK, reperfusion injury salvage kinase.


**Inhibiting MPTP opening to protect the heart against acute IRI**

The MPTP is a nonselective channel of the inner mitochondrial membrane, the opening of which mediates cell death by uncoupling oxidative phosphorylation and inducing mitochondrial swelling, resulting in ATP depletion and necrotic cell death. The molecular composition of the MPTP is not clear, although it has been suggested that ATP synthase and mitochondrial cyclophilin D are important components. In the setting of an acute myocardial infarction (AMI), it has been shown to remain closed during acute myocardial ischemia and to be open in only the first few minutes of reperfusion. Therefore, preventing its opening at the onset of reperfusion is an important therapeutic strategy for reducing myocardial infarct (MI) size after an AMI. Preventing MPTP opening at the onset of reperfusion can be achieved in various ways as follows:

1. **Directly** by pharmacological MPTP inhibition;
2. **Indirectly** through the activation of signaling pathways that converge on the MPTP;
3. **Indirectly** by modifying factors such as mitochondrial Ca2+ overload and ROS production, which are known to induce MPTP opening (see Figure 2).

**Signaling pathways underlying ischemic conditioning that target the MPTP**

The heart can be protected from the detrimental effects of acute IRI by subjecting it to brief non-lethal episodes of ischemia and reperfusion, a phenomenon that has been termed “ischemic conditioning.” Importantly, the protective stimulus can be applied directly to the heart before the index ischemic event (ischemic preconditioning) or at the onset of reperfusion (ischemic postconditioning) or it can be applied to an organ or tissue remote from the heart (remote ischemic conditioning). A number of different signal transduction pathways have been shown to mediate ischemic conditioning, including the reperfusion injury salvage kinase (RISK) pathway (comprising the PI3K-Akt and MEK1/2-Erk1/2), the survival activat-
ing factor enhancement (SAFE) pathway (comprising tumor necrosis factor α, JAK-STAT, and the nitric oxide [NO]-cyclic guanosine monophosphate [cGMP] pathway). These signaling cascades mediate the ischemic conditioning stimulus from the cell surface receptor to the mitochondria where they mediate cardioprotection by inhibiting MPTP opening (see Figure 2). The elucidation of these signaling pathways underlying ischemic conditioning has made it possible to use pharmacological agents to activate these signal mediators and recapitulate cardioprotection (Figure 2). Examples of RISK, SAFE, and NO-cGMP pathway activators that have been shown to protect the heart against acute IRI include growth factors and cytokines, such as atrial natriuretic peptide, insulin, erythropoietin, and glucagon-like peptide-1.

**Cyclosporin A: a direct inhibitor of the MPTP**

The immunosuppressant drug cyclosporin A (CsA) is a potent inhibitor of MPTP opening that has been demonstrated to reduce MI size in a number of experimental animal studies, but not all. This therapeutic strategy has been translated into the clinical setting in several phase 2 clinical trials in AMI, coronary artery bypass graft (CABG) surgery, and stroke, but the results have been mixed. The recently completed CYCLE trial (Cyclosporine E in reperfused acute myocardial infarction [NCT01650682]), which included 410 ST-segment elevation MI (STEMI) patients, also failed to demonstrate any benefits with CsA administered before primary percutaneous coronary intervention (PPCI), in terms of ST-segment resolution and enzymatically estimated MI size. Whether MPTP inhibition can improve clinical outcomes has been recently tested in the CIRCUS trial (does Cyclosporine ImpRove Clinical oUtcome in ST-elevation myocardial infarction patients), which involved 970 patients. In that trial, it was shown that the administration of CsA immediately before PPCI failed to improve clinical outcomes at one year (all-cause death, heart failure hospitalization, and adverse LV remodeling) in anterior STEMI patients. Why this large phase 3 trial did not confirm the positive results reported in previous phase 2 studies remains unclear, but potential reasons include the following:

1. A possible type I error observed in small-size clinical studies;
2. Off-target effects of CsA, as CsA is known to inhibit cyclophilin A and calcineurin, of which some may have counteracted the benefit of inhibiting MPTP opening; and, perhaps, changes in STEMI patients since the initial phase 2 trial, including a greater use of the new P2Y12 platelet inhibitors (prasugrel, ticagrelor), which are known to reduce MI size per se.

**TRO40303: an indirect inhibitor of the MPTP**

TRO40303 binds to the translocator protein TSPO in the outer mitochondrial membrane and is believed to inhibit MPTP opening by attenuating ROS production. It has been reported in small animal experimental studies to reduce MI size, but the cardioprotective effect was not replicated in a clinically relevant porcine MI model. In the 163-STEMI-patient MITOCARE study (which investigated the efficacy and safety of TRO40303 for reduction in reperfusion injury in patients undergoing revascularization for STEMI), this agent failed to reduce MI size when administered at the time of PPCI, despite careful patient selection (completely occluded infarct-related artery, large area at risk [AAR]). The neutral findings of the MITOCARE study may be due in part to ambiguous cardioprotective effects previously revealed in experimental studies and the fact that the formulation and dosage of TRO40303 used in the clinical study differed from that in experimental studies. Finally, more adverse events were reported in patients administered TRO40303 than in the placebo arm, thereby limiting the clinical application of this therapeutic approach.

**MTP-131 and myocardial energetics**

MTP-131, a mitochondria-targeting peptide, has been shown to optimize mitochondrial energetics and attenuate the production of ROS by selectively targeting cardiolipin in the inner mitochondrial membrane. It has been reported in both small and large animal experimental studies to reduce MI size when administered at the onset of reperfusion and to prevent adverse LV remodeling after MI. However, in the EMBRACE STEMI clinical trial (Evaluation of Myocardial effects of Bendavia for reducing Reperfusion injury in patients with Acute Coronary Events), intravenous MTP-131 administered before PPCI failed to reduce enzymatically estimated MI size in a carefully selected population of anterior STEMI patients (ischemic time <4 hours, no collateral vessels, and fully occluded coronary artery). The reasons for the neutral results of this study are not known, but potential reasons may include a single-targeted approach to cardioprotection, or pharmacokinetic or pharmacodynamic difficulties in targeting mitochondria in STEMI patients.

**Metabolic modulation to protect the heart against acute IRI**

Improving myocardial energetics by modulating mitochondrial metabolism is an important strategy for cardioprotection that has been extensively investigated over the last 30 to 40 years. In 1970, Lionel Opie first used insulin to promote glucose oxidation to protect the heart against acute myocardial ischemia. This metabolic approach to protecting the ischemic heart underlies the cardioprotective effects of trimetazidine.

**Trimetazidine and metabolic modulation**

Trimetazidine is known to improve myocardial glucose utilization by inhibiting fatty acid metabolism. It does this by inhibiting long-chain 3-ketoacyl-coenzyme A thiolase, thereby blocking β-oxidation of fatty acids and promoting glucose oxidation. In the ischemic heart, where oxygen is scarce, glucose oxidation is more beneficial than fatty acid oxidation as the former requires less oxygen consumption than the latter. This metabolic effect of trimetazidine is central to its antianginal effects in patients with stable coronary artery disease (CAD).
A number of experimental studies have shown that trimetazidine can protect the heart against acute IRI, as evidenced by reductions in MI size when administered as a pretreatment and when administered at the onset of reperfusion. This therapeutic approach has been investigated in patients presenting with an AMI in the large EMIP-FR clinical trial (European Myocardial Infarction Project—Free Radicals), and although it did not improve clinical outcomes in AMI patients reperfused by thrombolysis, it appeared to have a beneficial effect in non-reperfused patients, underscoring its anti-ischemic effect.

Recent meta-analyses have shown that it can decrease perioperative and periprocedural myocardial injury in patients undergoing coronary revascularization by CABG surgery and PCI, respectively, suggesting it has a cardioprotective effect in these clinical settings. The beneficial effects from modulating mitochondrial metabolism may also be helpful in heart failure, another condition in which disturbances in mitochondrial metabolism play an important role.

**Ivabradine and myocardial energetics**

Another effective approach to cardioprotection is to reduce the myocardial energy requirements of the heart during acute IRI. This can be achieved with little hemodynamic consequence by the drug ivabradine, which by inhibiting the If current in the sinus node can induce a selective lowering of heart rate. This drug has been demonstrated to lower heart rate and reduce myocardial ischemia in several experimental studies. However, whether the anti-ischemic effect of ivabradine is secondary to heart rate lowering is not clear, and recent experimental studies have found that this drug can protect the heart against acute IRI in paced animal hearts, suggesting beneficial pleiotropic effects of this drug, which may include attenuation of ROS production and inhibition of MPTP opening in response to acute IRI. Further experimental studies are required to elucidate the mechanisms underlying the cardioprotective effect of ivabradine.

In the clinical setting, by lowering heart rate to reduce myocardial oxygen consumption and increase coronary blood flow, ivabradine has been shown to be an effective antianginal agent in patients with stable CAD. However, this therapeutic approach did not improve clinical outcomes in a group of such patients without heart failure. In contrast, it has been shown to improve clinical outcomes (less cardiovascular mortality or heart failure hospitalization) in stable CAD patients with heart failure and heart rates above 70 beats per minute.

**Summary and conclusions**

Mitochondria lie at the heart of a number of cardioprotective signaling pathways underlying ischemic conditioning. As such, a variety of pharmacological treatment strategies aimed at protecting mitochondria against the detrimental effects of acute myocardial IRI have been investigated in both experimental and clinical studies, with mixed results. Of these strategies, the current treatments that are already in clinical practice include trimetazidine and ivabradine—further studies are required to elucidate the benefit of these agents in acute myocardial IRI and in improvement of clinical outcomes in patients with ischemic heart disease.

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C O N T E M P O R A R Y T R E A T M E N T O F A N G I N A

Keywords: cardioprotection; ischemia; ischemic conditioning; mitochondria; therapeutic target; trimetazidine

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Mitochondria as a therapeutic target in ischemia – Hausenloy

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**La mitochondrie, cible thérapeutique dans l’ischémie**

La maladie coronaire est la cause principale de décès et d’invalidité dans le monde. Il est donc urgent de trouver de nouvelles cibles thérapeutiques pour protéger le cœur des effets délétères des lésions aiguës d’ischémie/reperfusion afin de préserver la fonction cardiaque et d’améliorer les résultats cliniques chez les patients coronariens. À cet égard, les mitochondries, qui sont les « centrales énergétiques » de la cellule et représentent le tiers du volume d’un cardiomyocyte, sont une cible importante pour la cardioprotection. La compréhension des voies de signalisation sous-tendant le phénomène endogène de cardioprotection du conditionnement ischémique, par lequel le cœur peut être protégé par des épisodes brefs non létaux d’ischémie et de reperfusion, a permis d’établir que la mitochondrie est l’effecteur terminal dans beaucoup de voies de transduction des signaux. Dans cet article, nous examinons la mitochondrie en tant que cible pour la protection du cœur contre les lésions d’ischémie/reperfusion, une approche dont l’application thérapeutique pourrait aider à améliorer les résultats cliniques des patients coronariens.
In the healthy human heart, free fatty acids (FFAs) supply approximately 60% to 90% of the energy used to synthesize adenosine triphosphate (ATP); 10% to 40% comes from glucose and lactate. During ischemia, reduced delivery of oxygen to cardiomyocytes leads to a decrease in ATP formation by oxidative phosphorylation, an increase in the rate of glycolysis, and a high rate of conversion of pyruvate to lactate. This metabolic disturbance yields a disruption in cell homeostasis (with accumulation of lactate and H+ ions), a fall in intracellular pH, and a reduction in contractile work. A metabolic shift by direct inhibition of FFA oxidation in the mitochondria with trimetazidine results in a decrease in the frequency of angina attacks, increased exercise tolerance, improvement in quality of life, enhanced myocardial contractility in patients with left ventricular dysfunction, and reduced myocardial damage during myocardial revascularization procedures. The European Society of Cardiology guidelines on stable angina indicate that trimetazidine may be considered second-line for the treatment of angina/relief of ischemia in patients already receiving a β-blocker and/or calcium channel antagonist to control symptoms. With a different view, the Brazilian guidelines on stable angina recommend trimetazidine for symptom relief as an add-on therapy right after β-blockers, but before long-acting nitrates (unless there is a need for better blood pressure control, in which case calcium channel antagonists are preferable). The less traditional view held by the Brazilian Society of Cardiology recognizes that trimetazidine may be offered early on—before long-acting nitrates—in combination with any hemodynamic agent, as long as blood pressure and heart rate are properly controlled. With this latter position, a different view emerges of the treatment of patients with stable IHD, one that widens the concept of “optimal medical therapy” and allows for the inclusion of trimetazidine before the commonplace “after everything else has failed” stance.”

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When William Heberden first named and described angina pectoris in 1772, its treatment appeared the stuff of far-off dreams: “(...) With respect to the treatment of this complaint, I have little or nothing to advance: nor indeed is it to be expected we should have made much progress in the cure of a disease, which has hitherto hardly had a place or a name in medical books.”1 How times have changed. Since the description more than 250 years ago of the clinical presentation of an entity of which William Heberden could “not recollect any mention among medical authors,”1 and for which he “had little or nothing to advance” regarding its treatment, the modern cardiologist now faces a completely different challenge: that of devising an adequate therapeutic strategy for patients with stable angina using the many options available, which include antianginal drugs and myocardial revascularization procedures (percutaneous or surgical). But for physicians of the past the treatment scenario was very different: it took almost a century after Heberden’s description before the Scottish physician Sir Thomas Brunton2 first used amyl nitrite in the treatment of angina pectoris in 1867. “In angina...
pectoris we wish a drug which will relax spasm of the vessels very quickly, but as a rule we do not require the relaxation to be prolonged," said Brunton of the type of pharmacological effect he thought would be useful.3 While Brunton was using amyl nitrite, another British physician, William Murrell, began using nitroglycerine in the treatment of angina pectoris.4 After almost a century during which the use of nitrates had gained wide popularity as the only medical treatment for angina, there were two important new arrivals in the twentieth century: β-blockers5 (early-1960s) and calcium channel antagonists6 (late-1960s to mid-1970s). These drugs formed the new medical management basis for symptom relief in patients with stable angina; they could either be used alone or in combination, as tolerated, in the absence of contraindications to their use.

Although many patients certainly benefited from a combination of these so-called hemodynamic agents, it later became apparent that others remained symptomatic despite the use of maximally tolerated doses of these drugs. Moreover, even after an increase in the use of myocardial revascularization procedures, including a boom in the number of percutaneous coronary interventions (PCIs), patients would remain free of angina for different lengths of time, only to return a couple of years later complaining of angina again. In the randomized trial MASS (Medicine, Angioplasty, or Surgery Study) II,7 for example, in patients with nonlimiting angina, multivessel disease, and preserved left ventricular function at baseline, 45% of those initially assigned to optimal medical therapy (a combination of β-blockers and/or long-acting nitrates and/or calcium channel antagonists) were still symptomatic after 5 years of follow-up; however, it should be noted that even for those who were assigned to a myocardial revascularization procedure, the prevalence of angina was 22% (PCI group) and 25% (surgical group). In the COURAGE (Clinical Outcomes Utilizing Revascularization and AGgressive drug Evaluation) trial,8 in which optimal medical therapy with or without PCI was offered to patients with stable angina, about 40% of patients were still complaining of angina after 3 years of follow-up, regardless of the therapeutic strategy assigned. These observations, which are not unique in the literature, raised the question, "When it comes to offering optimal symptom control, what is true ‘optimal medical therapy’ in patients with stable angina?" This led to an intensive search for drugs with alternative mechanisms of action to hemodynamic modulation to be added to the therapeutic armamentarium for the management of patients with ischemic heart disease (IHD).

Optimizing energy metabolism as a therapeutic target in patients with angina

Even though angina is regarded as the clinical hallmark of coronary artery disease (CAD), as so eloquently described by Heberden, myocardial ischemia cannot be considered an event precisely circumscribed by the onset and resolution of angina. In fact, the identification of an ischemic cascade of pathophysiologic events9 broadened not only our understanding of different clinical presentations of CAD, but also opened up opportunities for new therapeutic strategies. Figure 1 shows the temporal sequence of ischemic events during stress-induced myocardial ischemia.10

**Figure 1. Temporal sequence of ischemic events during stress-induced myocardial ischemia. Note that after perfusion heterogeneity sets in, metabolic alteration appears before any detectable functional abnormality. Chest pain is usually the latest manifestation of ongoing myocardial ischemia.**

**Abbreviation:** ECG, electrocardiography.


**SELECTED ABBREVIATIONS AND ACRONYMS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>3-KAT</td>
<td>3-ketoacyl coenzyme A thiolase</td>
</tr>
<tr>
<td>ATP</td>
<td>adenosine triphosphate</td>
</tr>
<tr>
<td>CAD</td>
<td>coronary artery disease</td>
</tr>
<tr>
<td>COURAGE</td>
<td>Clinical Outcomes Utilizing Revascularization and AGgressive drug Evaluation</td>
</tr>
<tr>
<td>EMA</td>
<td>European Medicines Agency</td>
</tr>
<tr>
<td>FFA</td>
<td>free fatty acid</td>
</tr>
<tr>
<td>IHD</td>
<td>ischemic heart disease</td>
</tr>
<tr>
<td>MASS</td>
<td>Medicine, Angioplasty, or Surgery Study</td>
</tr>
<tr>
<td>PCI</td>
<td>percutaneous coronary intervention</td>
</tr>
</tbody>
</table>

**Basic concepts in heart metabolism**

Because metabolic disturbances occur early on during myocardial ischemia, the clinician should bear in mind basic concepts related to heart metabolism. In the healthy human heart, free fatty acids (FFAs) supply approximately 60% to 90% of the energy used to synthesize adenosine triphosphate (ATP), whereas the remaining 10% to 40% of the ene-
gy comes from different energetic substrates, ie, glucose and lactate. Once in the mitochondrion, FFAs undergo \( \beta \)-oxidation, a complex multistep enzymatic process, to produce ATP for contractile work, calcium uptake by the sarcoplasmic reticulum, and ion homeostasis. Glucose is taken up by the myocardium and is either stored as glycogen or broken down by glycolysis to pyruvate in the cytosol of the cell. Pyruvate is oxidized to acetyl-CoA in the mitochondria by the enzyme pyruvate dehydrogenase. Oxidation of glucose and lactate is strongly inhibited by high rates of FFA oxidation in the heart (Figure 2).11

Heart metabolism during ischemia
Reduced oxygen delivery to cardiomyocytes during ischemia leads to mitochondrial metabolic dysfunction, resulting in a decrease in ATP formation by oxidative phosphorylation and an increase in the rate of glycolysis. Pyruvate produced by glycolysis is not so readily oxidized in the mitochondria, which allows a high rate of conversion of pyruvate to lactate in the cytosol and a consequent rise in tissue lactate levels. This metabolic disturbance seen during myocardial ischemia yields a dramatic disruption in cell homeostasis, with accumulation of lactate and H\(^+\) ions, a fall in intracellular pH, and a reduction in contractile work (Figure 3).11

Targeting FFA and carbohydrate oxidation in IHD
Direct inhibition of FFA oxidation in the mitochondria with the 3-ketoacyl coenzyme A thiolase (3-KAT) inhibitor trimetazidine results in an increase in the rates of glucose and/or lactate uptake and oxidation. The suppression of FFA oxidation and increased oxidation of pyruvate by pyruvate dehydrogenase in the mitochondria reduces ischemia-induced disruption of cardiac metabolism. In other words, inhibiting cardiac FFA oxidation and increasing the oxidation of pyruvate results in less lactate production and a fall in cell \( \text{pH} \), resulting in clinical benefit for the ischemic patient. This direct metabolic approach is optimally suited to conditions in which there is sufficient residual oxygen delivery to the myocardium to support pyruvate oxidation in the mitochondria. In other words, it is important that there be a sufficient rate of acetyl-CoA oxidation and oxygen consumption so that increasing the rate of pyruvate oxidation has a meaningful effect on the rate of lactate production. This metabolic shift from FFA oxidation to glucose oxidation has proven effective in different scenarios in patients with IHD and/or heart failure.

Clinical benefits of trimetazidine in patients with stable angina
Back in the late 1960s, the use of trimetazidine in patients with angina pectoris had been proposed and successfully used in small series of patients, although the exact mechanism of action implicated in pain relief was not clear at that time. Later on, the effects of trimetazidine were compared with those of propranolol in a double-blind parallel group multicenter study in 149 men with stable angina. After 3 months, simi-
objective (increase in exercise tolerance assessed during a
treadmill test) evidence for its role in the management of pa-
tients with stable angina not sufficiently controlled with a sin-
gle hemodynamic agent.

Since most clinical trials of trimetazidine involved a limited
number of patients, a recently published study looked at 13
randomized controlled trials comprising 1628 patients to de-
termine the efficacy of trimetazidine combined with other anti-
anginal drugs versus other antianginal drugs in the treatment
of stable angina pectoris. Figure 4 (page 268) shows that the
weekly mean number of angina attacks decreased (panel A)
and exercise duration improved (panel B) in patients receiving
trimetazidine on top of conventional antianginal therapy.24

Trimetazidine in patients with stable angina:
what do the guidelines say?
The unequivocal benefits of trimetazidine in patients with sta-
bile IHD include: (i) a decrease in the frequency of angina at-
tacks and in the need for short-acting nitrates for pain relief;44
(ii) increased exercise tolerance;25, (iii) improvement in quality
of life;26 (iv) enhanced myocardial contractility in patients with
left ventricular dysfunction;27 and (v) a reduction in myocardial
damage during myocardial revascularization procedures, such
as angioplasty19 or bypass surgery.28 In terms of cardiovascu-
lar events, trimetazidine may decrease the risk of hospital-
izations in patients with heart failure;30 the use of trimeta-
didine has been linked to a lower risk of death in patients after
an acute myocardial infarction31 and in patients with heart fail-
ure.30,32 So, how do different medical societies value these ben-
efits and incorporate trimetazidine in their guidelines on sta-
bile angina?

◆ The European perspective
The most recent guidelines on stable angina issued by the
European Society of Cardiology33 acknowledge trimetazidine
as an anti-ischemic metabolic modulator with similar antiang-
inal efficacy to propranolol and devoid of any discernible he-
modynamic action. In June 2012, the European Medicines
Agency (EMA) reviewed available data regarding its efficacy
in effort-induced myocardial ischemia.34 A thorough analysis
of the safety and effectiveness of trimetazidine carried out by
the EMA concluded that the drug was safe, although move-
ment disorders (including Parkinsonism), which were uncom-
mon and reversible after drug discontinuation, could not be
excluded with the use of trimetazidine. Thus, in patients with
angina pectoris, treatment with trimetazidine should be con-
sidered as an add-on to existing treatments in those who are
not adequately controlled by, or who are intolerant to, oth-
er medicines for angina pectoris. Accordingly, the European
guidelines stated that trimetazidine may be considered for
the second-line treatment of angina/relief of ischemia in pa-
tients already receiving a β-blocker and/or calcium channel
antagonist to control symptoms (class of recommendation:
IIb; level of evidence: B).33

◆ The North American perspective
Although trimetazidine is not marketed in the United States,
its ability to improve cellular tolerance to ischemia, delay the
onset of exercise-induced ischemia, and reduce angina epi-
sodes and nitroglycerin use has been recognized by US ex-
erts in the American College of Cardiology/American Heart
Association guidelines on the management of patients with
stable angina.35

◆ The Brazilian perspective
Trimetazidine is marketed worldwide and, therefore, included
in different national guidelines for the management of patients
with stable CAD or stable angina. Because a detailed North
American reference to its use is lacking, many countries
around the world where trimetazidine is available follow the
recommendations proposed by the European Society of Car-
diology. The Brazilian Society of Cardiology, however, has tak-
en a slightly different approach in its placement of trimetazi-
dine in the treatment of patients with stable angina.

In the most recent version of the Brazilian guidelines on stable
angina,36 β-blockers have kept their position as the first-line
treatment for the prophylaxis of angina attacks and short-
acting nitrates remain the cornerstone treatment for the im-
mediate relief of chest pain due to CAD. But for patients whose
symptoms are poorly controlled with β-blockers, the Brazilian
guidelines now recommend that physicians consider adding
trimetazidine early on, provided blood pressure and heart rate
have been controlled. However, if one needs better control
of blood pressure calcium channel antagonists may be pre-
ferred.

There are a couple of studies that may support this approach.
In these studies, the effects of early administration of trimeta-
didine on top of different background antianginal therapies
were assessed. In one study, 53 patients with symptomatic
stable angina receiving propranolol 40 mg tid were random-
ized to long-acting nitrates or trimetazidine as an add-on ther-
apy for 6 weeks.37 Patients on the combination of a β-blocker
and long-acting nitrates had a 30% reduction in the number
of angina episodes per week compared to a 62% reduction
seen in patients on the β-blocker + trimetazidine combina-
tion (P=0.001). A treadmill test revealed that the latter com-
bination yielded a 6-fold increase in total exercise duration
(95 s versus 16 s).

In another study, investigators looked at the benefit of adding
trimetazidine in 1213 highly symptomatic patients with sta-
ble angina being treated with different antianginal strate-
gies, comprising β-blocker alone, β-blocker + long-acting
nitrates, or β-blocker + calcium channel antagonist.38 The ad-
dition of trimetazidine significantly reduced the weekly num-
ber of angina attacks and consumption of short-acting ni-
trates in all patients, regardless of the treatment strategy used.
But, maybe more importantly, the combination of long-acting
A. Weekly number of angina attacks

<table>
<thead>
<tr>
<th>Study ID</th>
<th>WMD (95% CI)</th>
<th>%</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 8 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Andreas (1997)</td>
<td>-1.20 (-1.56, -1.10)</td>
<td></td>
<td>10.13</td>
</tr>
<tr>
<td>Gang Zhang (2008)</td>
<td>-1.20 (-2.64, 0.24)</td>
<td>3.72</td>
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<tr>
<td>Ribeiro (2007)</td>
<td>-1.10 (-2.03, -0.17)</td>
<td>5.86</td>
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<tr>
<td>Dengyun Yang (2011)</td>
<td>-1.40 (-2.28, -0.53)</td>
<td>6.25</td>
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<tr>
<td>Subtotal (I-squared=0.0%, p=0.971)</td>
<td>-1.29 (-1.48, -1.11)</td>
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<tr>
<td>≥ 12 weeks</td>
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<td></td>
<td></td>
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<tr>
<td>Szwed (2001)</td>
<td>-1.20 (-1.93, 0.47)</td>
<td>7.18</td>
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<tr>
<td>Changqing Liang (2004)</td>
<td>0.47 (0.24, 0.69)</td>
<td>10.04</td>
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<td>Jianhua Xu (2005)</td>
<td>-1.05 (-1.29, -0.81)</td>
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<td>Lixin Ren (2008)</td>
<td>-1.01 (-1.33, -0.69)</td>
<td>9.60</td>
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<tr>
<td>Yun Zheng (2010)</td>
<td>-1.40 (-2.20, -0.60)</td>
<td>6.70</td>
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</tr>
<tr>
<td>Guangrong Zhou (2010)</td>
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<td>9.95</td>
<td></td>
</tr>
<tr>
<td>Helyun Lin (2013)</td>
<td>-0.70 (-0.86, -0.54)</td>
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<tr>
<td>Subtotal (I-squared=95.2%, p=0.000)</td>
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<td>Jiang Li (2013)</td>
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<td>Subtotal (I-squared=0%, p=1.000)</td>
<td>-1.13 (-1.38, -0.86)</td>
<td>10.22</td>
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<tr>
<td>Overall (I-squared=93.8%, p=0.000)</td>
<td>-0.95 (-1.30, -0.61)</td>
<td>100.00</td>
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</tbody>
</table>

NOTE: Weights are from random effects analysis

B. Exercise duration

<table>
<thead>
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<th>Study ID</th>
<th>WMD (95% CI)</th>
<th>%</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 8 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Szwed (2001)</td>
<td>27.00 (-0.02, 54.02)</td>
<td>38.84</td>
<td></td>
</tr>
<tr>
<td>Gang Zhang (2006)</td>
<td>27.00 (-26.88, 80.88)</td>
<td>22.87</td>
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<tr>
<td>Subtotal (I-squared=0.0%, p=1.000)</td>
<td>27.00 (2.85, 51.15)</td>
<td>61.71</td>
<td></td>
</tr>
<tr>
<td>≥ 12 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jianhua Xu (2005)</td>
<td>67.50 (8.41, 126.59)</td>
<td>20.58</td>
<td></td>
</tr>
<tr>
<td>Yun Zheng (2010)</td>
<td>108.70 (42.06, 175.35)</td>
<td>17.71</td>
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<tr>
<td>Subtotal (I-squared=0.0%, p=0.386)</td>
<td>85.65 (41.42, 129.85)</td>
<td>38.29</td>
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<td>Overall (I-squared=50.2%, p=0.110)</td>
<td>49.81 (15.04, 84.57)</td>
<td>100.00</td>
<td></td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis

Figure 4. Forest plot for the aggregate weekly mean number of angina attacks (panel A) and exercise duration at peak exercise (panel B) in patients received trimetazidine combined with conventional antianginal agents in the treatment of stable angina pectoris, in comparison with conventional antianginal agents.

nitrates or calcium channel antagonists with β-blockers did not provide any additional reduction in the number of angina attacks compared with patients receiving β-blocker + trimetazidine.

So, when the time came to review the Brazilian guidelines on stable angina, the committee decided to give trimetazidine a class IIa recommendation (level of evidence; B) for symptoms relief as a second-line treatment, as an add-on therapy right after β-blockers (unless, as previously stated, there is a need for better blood pressure control, in which case calcium channel antagonists are preferable).

Another particular aspect of this document is that long-acting nitrates have been downgraded to a third-line treatment for angina control. The reason being that at least two studies have demonstrated that the long-term use of long-acting nitrates leads to an increase in the risk of cardiovascular events, including death, in healed myocardial infarction patients and in diabetes patients who underwent elective PCI.40 Worsening of endothelial dysfunction is a potential complication of long-acting nitrates that may be linked to adverse outcomes.41

Conclusion

The benefits of trimetazidine in patients with cardiovascular disease have been demonstrated in several studies and meta-analyses, allowing for its incorporation into practice guidelines not only for stable angina, but also for heart failure. Although there is some consistency in the view of trimetazidine’s use as an add-on agent, there is a slight difference in perception about how soon trimetazidine should be added as a second-line treatment. The more traditional view—expressed by the European Society of Cardiology, for instance—recommends trimetazidine as a second-line agent for use only when a combination of conventional hemodynamic agents, such as β-blockers and calcium channel antagonists, has been unable to control symptoms satisfactorily. On the other hand, the less traditional view held by the Brazilian Society of Cardiology recognizes that trimetazidine, which possesses no major safety concerns, may be offered early on—for long-acting nitrates—in combination with any hemodynamic agent (β-blocker and/or calcium channel antagonist), as long as blood pressure and heart rate are properly controlled.

With this latter position, a different view emerges of the treatment of patients with stable IHD, one that widens the concept of “optimal medical therapy” and allows for the inclusion of trimetazidine before the commonplace “after everything else has failed” stance. This proposal may seem original and new, but it was, in fact, prophetically suggested almost 50 years ago by two British investigators, who said that “trimetazidine appears to have a place in the long-term treatment of angina pectoris (...), and may be given to all cases of angina.”42 It is never too late to do what we ought to have done.

References


The place of metabolic agents in contemporary coronary artery disease guidelines – Gowdak MEDICOGRAPHIA, Vol 38, No 3, 2016 269
La place des agents métaboliques dans les recommandations actuelles sur la maladie coronaire

Dans le cœur humain sain, les acides gras libres (AGL) fournissent environ 60 % à 90 % de l’énergie utilisée pour synthétiser l’ATP (adénosine triphosphate) ; 10 % à 40 % viennent du glucose et du lactate. Pendant l’ischémie, la réduction de l’apport en oxygène aux cardiomocytes conduit à une diminution de la formation d’ATP par phosphorolysis oxydative, à une augmentation du taux de la glycolyse et à un taux élevé de conversion du pyruvate en lactate. Ce trouble métabolique provoque une perturbation de l’homéostasie cellulaire (avec l’accumulation de lactate et d’ions H+), une chute du pH intracellulaire et une réduction du travail contractile. Avec la trimétazidine, un transfert métabolique par inhibition directe de l’oxydation des AGL dans la mitochondrie diminue la fréquence des crises d’angor, majore la tolérance à l’effort, améliore la qualité de vie, augmente la contractilité myocardique des patients ayant une dysfonction ventriculaire gauche et diminue les lésions myocardiques pendant les procédures de revascularisation myocardique. D’après les recommandations de la Société Européenne de Cardiologie sur l’angor stable, la trimétazidine peut être utilisée en seconde ligne pour le traitement de l’angor ou le soulagement de l’ischémie chez les patients recevant déjà un β-bloquant et/ou un antagoniste calcique pour contrôler les symptômes. Voyant les choses différemment, les directives brésiliennes sur l’angor stable recommandent la trimétazidine pour le soulagement des symptômes comme traitement d’appoint juste après les β-bloquants (sauf s’il faut un meilleur contrôle de la pression artérielle, auquel cas les antagonistes calciques sont préférables), mais avant les dérivés nitrés à longue durée d’action.
The onset of an angina pectoris attack is associated with dramatic alterations in cardiac energy metabolism. A mismatch between oxygen (O$_2$) demand and O$_2$ supply to the heart muscle results in a decrease in mitochondrial oxidative metabolism, leading to an energy-deficient state in the heart. In addition, changes in the source of substrates for cardiac mitochondrial energy metabolism contribute to contractile dysfunction and to a decrease in cardiac efficiency. These changes include an increase in the contribution of cardiac fatty acid (FA) oxidation to residual mitochondrial oxidative metabolism and an uncoupling of glycolysis from glucose oxidation. Revascularization can lessen angina symptoms predominantly by lessening the mismatch between O$_2$ demand and O$_2$ supply to the heart muscle. However, while revascularization can improve O$_2$ supply, some of the switches in cardiac metabolism persist after revascularization. In particular, the muscle becomes overly reliant on FA oxidation as a source of energy, primarily at the expense of glucose oxidation. This can continue to uncouple glycolysis from glucose oxidation, resulting in a continued decrease in cardiac efficiency. As a result, a challenge in revascularized angina patients is to normalize cardiac energy metabolism and improve cardiac efficiency. Recent evidence suggests that therapeutically regulating cardiac energy metabolism by reducing FA oxidation—which increases glucose oxidation—can improve cardiac efficiency and cardiac function and lessen the symptoms of angina, even in revascularized patients. In this article, we review the cardiac mitochondrial energy metabolic changes that occur in the heart in angina patients, and the changes that occur during revascularization, as well as the potential for targeting FA oxidation to treat angina, both in the presence or absence of revascularization.

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Angina pectoris due to coronary artery disease (CAD) is a major health problem in the world. Revascularization of angina patients, either by percutaneous coronary interventions (PCI) or by coronary artery bypass graft (CABG) surgery, can substantially improve angina symptoms for most patients. However, symptoms of angina can persist and may return over time, even when taking optimal antianginal medications. As a result, it is imperative to identify new approaches to treat angina, even in the revascularized patient. One potentially promising approach to treating angina is to optimize cardiac energy metabolism. This would appear to be a logical approach, as a decrease in oxygen availability and alterations in cardiac energy metabolism are prominent changes in the angina patient. However, in
order to fully exploit the potential of optimizing cardiac energy metabolism in angina patients, it is first important to understand how cardiac energy metabolism is regulated in the normal patient, in the angina patient, and after revascularization of the angina patient. This paper reviews the cardiac metabolic changes that occur in the angina patient, and how optimizing cardiac energy metabolism can be used as an approach to treat such patients, both those with or without revascularization.

**Cardiac energy metabolism in the normal heart**

The heart has a very high energy demand, due to the need to produce large amounts of adenosine triphosphate (ATP) to support the continuous contractile function of the heart. There are no significant energy reserves in the heart, and there is a near complete turnover of the myocardial ATP pool every 5 to 10 seconds. To meet these high energy demands, the heart generates ATP by metabolizing a variety of energy substrates, including fatty acids, glucose, lactate, ketone bodies, and amino acids (Figure 1). The contributions of each of these energy substrates to ATP generation are tightly regulated, and there is a significant degree of plasticity and interdependence in the use of these energy substrates. Under normal, physiological conditions, fatty acids and carbohydrates (ie, glucose and lactate) represent the primary metabolic fuels that sustain cardiac function, and upwards of 95% of ATP production is attributable to mitochondrial oxidative phosphorylation. The remainder of this ATP production primarily originates from glycolysis, which has the benefit of producing ATP without the need for oxygen (Figure 1). The tradeoff of this anaerobic ATP production is that lactate and protons (H’+s) are two of the metabolic byproducts of glycolysis if the pyruvate produced from glycolysis is not subsequently subjected to mitochondrial oxidative metabolism. The heart normally displays substantial metabolic flexibility, with fatty acid and glucose metabolism having a considerable degree of interdependence, a process referred to as the Randle Cycle or the glucose/fatty acid cycle. Increasing fatty acid oxidation in the heart decreases glucose oxidation, whereas increasing glucose oxidation inhibits fatty acid oxidation. A key site at which fatty acid oxidation decreases glucose metabolism is at the level of pyruvate dehydrogenase (PDH), the rate-limiting enzyme for glucose oxidation. High rates of fatty acid oxidation inhibit PDH, secondary to activating a PDH kinase that phosphorylates and inhibits PDH.

**Cardiac energy metabolism in angina**

Various cardiac pathophysiological states cause perturbations of the tightly regulated pathways of myocardial energy substrate metabolism, and these perturbations contribute to the progression of myocardial injury. In CAD, repeated oxygen (O2) supply and demand mismatches results in downregulation of mitochondrial oxidative metabolism, and an increase in glucose uptake and glycolysis. During an angina attack, where O2 availability is not sufficient to meet the O2 requirements of the heart, impaired mitochondrial oxidative metabolism results in a rapid decline in ATP production from fatty acid oxidation and glucose oxidation that is proportional to the degree of ischemia (Figure 2A). Glycolysis becomes a very important source of energy during ischemia due to its ability to generate ATP in the absence of O2. During periods of mild-to-moderate ischemia, glucose uptake and the mobilization of endogenous glucose from stored glycogen contribute to increased flux through the glycolytic pathway. Despite the presence of ischemia, mitochondrial fatty acid oxidation remains the predominant source of residual oxidative metabolism. This is due to a number of ischemia-induced changes, which include the following: (i) an increase in circulating fatty acids to which the heart is exposed; (ii) an increase in myocardial fatty acid uptake; and (iii) an increase in mitochondrial fatty acid uptake (see Lopaschuk et al for re-
view). The increase in the relative contribution of fatty acid oxidation to mitochondrial oxidative metabolism results in a parallel decrease in glucose oxidation during ischemia. Since glycolysis is accelerated during ischemia, the hydrolysis of glycolytically derived ATP uncoupled from subsequent pyruvate oxidation leads to an increased generation of lactate and H+ (Figure 2A). In severely ischemic hearts, this can result in a decrease in pH in the myocardium, which can lead to cell death. In milder ischemia (such as seen during angina), the production of H+ from glycolysis leads to disturbances in ion homeostasis, which leads to a decrease in cardiac efficiency, as ATP is required to restore these ionic imbalances.

Cardiac energy metabolism after revascularization

Revascularization is an important approach to reducing the myocardial O2 supply and demand mismatch that can occur in the CAD patient. However, during revascularization, the short complete interruptions of blood flow produce a profound ischemia, which are accompanied by dramatic alterations in cardiac energy metabolism. During reperfusion of the ischemic heart, overall cardiac fatty acid oxidation rates are elevated, due, at least partially, to elevated levels of circulating fatty acids (Figure 2B). In addition, the subcellular control of fatty acid oxidation is altered, such that fatty acid oxidation becomes deregulated. Elevated levels of circulating fatty acids combined with an increase in mitochondrial fatty acid uptake results in an increase in fatty acid oxidation rates during reperfusion, with a concomitant marked decrease in glucose oxidation rates (Figure 2B). This elevation in circulating fatty acids and cardiac fatty acid oxidation after restoration of blood flow can impair cardiac function and cardiac efficiency (Figure 2B). The decrease in glucose oxidation after revascularization can result in increased uncoupling of glycolysis from glucose oxidation and a subsequent increase in production of lactate and H+, which can decrease cardiac efficiency and impair heart function. As a result, a challenge in the revascularized angina patient is to normalize cardiac energy metabolism, particularly by increasing glucose oxidation rates.

While revascularization can improve cardiac function and decrease mortality risk, alterations in cardiac energetics can persist in the heart after revascularization. This includes persistent abnormalities in mitochondrial oxidative metabolism, as well as alterations in energy substrate preference by the heart. In particular, a continued increased reliance on fatty acid oxidation at the expense of glucose oxidation can occur after reperfusion, providing a challenge in the revascularized patient to restore normal cardiac energy metabolism.

Figure 2. Alterations in myocardial energy metabolism during ischemia and reperfusion.

During ischemia (A), glycolysis becomes the main source of energy production in the absence of or a decreased supply of oxygen. Fatty acids dominate as the substrate for residual oxidative metabolism due to increased plasma levels of fatty acids, as well as alterations in the subcellular control of fatty acid oxidation. During reperfusion (B), glycolytic rates remain high, while fatty acid oxidation dominates over glucose oxidation as the main source of oxidative metabolism. The dominant fatty acid oxidation rates during reperfusion inhibit glucose oxidation. The uncoupling of glycolysis from glucose oxidation leads to an increase in proton production, which ultimately leads to myocardial acidosis and calcium overload.

Abbreviations: I-IV, complexes I to IV in the electron transport chain; ADP, adenosine diphosphate; ATP, adenosine triphosphate; CoA, coenzyme A; CPT, carnitine palmitoyl transferase; H+, proton; H2O, water; LDH, lactate dehydrogenase; MPC, mitochondrial pyruvate carrier; O2, oxygen; PDH, pyruvate dehydrogenase; PDHK, pyruvate dehydrogenase kinase; TCA, tricarboxylic acid.
Targeting fatty acid oxidation to treat angina

Classically, the pharmacological treatment of angina patients has focused on the use of agents that alter systemic and/or cardiac hemodynamics. With increasing knowledge of the mechanisms regulating cardiac energy substrate metabolism, and with the understanding that alterations in such metabolism contribute to the severity of angina symptoms, the modulation and optimization of energy substrate metabolism represents a novel and promising area for therapeutic intervention in angina patients. In this regard, pharmacological agents that shift the balance between the oxidative utilization of fatty acid and glucose toward glucose oxidation have been an area of intense research activity. In particular, pharmacological agents that either inhibit fatty acid oxidation and/or stimulate glucose oxidation are promising anti-ischemic interventions (Figure 3).

Fatty acid oxidation can be inhibited directly by decreasing fatty acid uptake into the mitochondria or by inhibiting mitochondrial fatty acid oxidation. Fatty acid oxidation can also be inhibited indirectly by increasing glucose oxidation. Pharmacological inhibition of fatty acid oxidation with drugs that lower fatty acid levels, block mitochondrial fatty acid uptake, or directly inhibit fatty acid oxidation all have potential benefit in the setting of angina.

One drug that directly targets mitochondrial fatty acid oxidation is trimetazidine. Trimetazidine is a partial fatty acid oxidation inhibitor that competitively inhibits the fatty acid oxidation enzyme, long chain 3-ketoacyl coenzyme A thiolase. The inhibition of fatty acid oxidation is accompanied by an increase in glucose oxidation. This is beneficial in both ischemic myocardium during restoration of blood flow or in already revascularized myocardium, as the increased glucose oxidation decreases the production of H⁺’s arising from the uncoupling of glycolysis from glucose oxidation.

Results from clinical studies have confirmed the effectiveness of trimetazidine as an anti-ischemic agent. Treatment of angina with trimetazidine increases time to 1-mm ST segment depression as well as weekly nitrate consumption. Trimetazidine has been shown to have comparable effectiveness to propranolol in treating stable angina. Combination therapies stimulate glucose oxidation are promising anti-ischemic pharmacological agents that either inhibit fatty acid oxidation and/or increase glucose oxidation in the heart.

![Diagram of pharmacological targets](image_url)

**Figure 3.** Diagrams for pharmacological targets that decrease fatty acid oxidation and/or increase glucose oxidation in the heart. Abbreviations: I-IV, complexes I to IV in the electron transport chain; ADP, adenosine diphosphate; ATP, adenosine triphosphate; CoA, coenzyme A; CPT, carnitine palmitoyl transferase; DCA, dichloroacetate; F₁, proton; H₂O, water; LDH, lactate dehydrogenase; MPC, mitochondrial pyruvate carrier; O₂, oxygen; PDH, pyruvate dehydrogenase; PDHK, pyruvate dehydrogenase kinase; TCA, tricarboxylic acid.

Although classified as a late sodium current inhibitor, ranolazine is also a partial fatty acid oxidation inhibitor, which has been shown to inhibit fatty acid oxidation and reciprocally increase glucose oxidation and PDH activity. In experimental studies, ranolazine attenuates myocardial stunning, reduces infarct size, increases cardiac ejection fraction, increases stroke volume, and increases mechanical efficiency without increasing oxygen consumption. Clinically, ranolazine, as an anti-ischemic agent, has been shown to increase exercise capacity and time to 1-mm ST-segment depression, and reduce the number of weekly angina attacks and nitroglycerin consumption as a monotherapy or combined therapy. However, a recent study showed that ranolazine had no incremental benefit in angina or quality of life in patients with incomplete revascularization after PCI. β-Adrenoceptor antagonists (β-blockers) are classic drugs used in the setting of angina as anti-ischemic agents.
of angina. This class of drug is believed to exert an oxygen-sparing effect by a reduction in inotropic and chronotropic effects, thus reducing cardiac workload. However, blockade of β-adrenergic receptors decreases catecholamine-induced lipolysis and therefore decreases plasma fatty acid availability and extraction. As a result, part of the benefit of β-blockade in the setting of angina may occur secondary to decreased myocardial fatty acid oxidation. Indeed, carvedilol has been shown to reduce myocardial free fatty acid uptake by 57% in patients with heart failure.23

In addition to inhibiting fatty acid oxidation, directly increasing myocardial glucose oxidation may be another approach to optimizing energy metabolism in angina. Dichloroacetate (DCA) acts via direct stimulation of the mitochondrial PDH complex via the inhibition of the activity of PDH kinase. The improved coupling between glycolysis and glucose oxidation is believed to be the mechanism by which DCA exerts its cardioprotective effects.24 Experimental studies show that DCA is cardioprotective in the setting of ischemia and reperfusion (see Lopaschuk et al for review). However, clinical data on the use of DCA is scarce. In a small clinical study, where DCA was given to patients with CAD via intravenous infusion, improvements in left ventricular stroke volume were observed in the absence of changes in heart rate, left ventricular end diastolic pressure, or myocardial oxygen consumption.25 The poor potency and pharmacokinetic profile of DCA make it unlikely that this drug will ever be used clinically.

Conclusion
Alterations in cardiac energy metabolism are an important factor in the severity of angina in both the revascularized and nonrevascularized patient. Significant metabolic changes result in an increase in the contribution of fatty acid oxidation compared with glucose oxidation to cardiac energy production, that leads to a decrease in cardiac efficiency. A challenge in the revascularized angina patient is to normalize cardiac energy metabolism and to improve cardiac efficiency. Therapeutic strategies aimed at inhibiting fatty acid oxidation are one potential approach to optimizing energy metabolism in the angina patient. One such approach is to directly inhibit fatty acid oxidation with trimetazidine, which leads to an indirect increase in glucose oxidation in the heart. The subsequent improvement in cardiac efficiency is associated with beneficial effects of trimetazidine in decreasing angina symptoms, even in the revascularized patient.

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La survenue d’une crise d’angor s’associe à des perturbations considérables du métabolisme énergétique cardiaque. Un déséquilibre entre besoins et apports en O₂ au niveau du muscle cardiaque entraîne une diminution du métabolisme oxydatif mitochondrial, aboutissant à un état de déficit énergétique dans le cœur. De plus, des modifications de la source des substrats du métabolisme énergétique mitochondrial cardiaque contribuent à une dysfonction contractile et à une diminution de l’efficacité cardiaque. Parmi ces modifications on compte une augmentation de la contribution de l’oxydation des acides gras au métabolisme oxydatif mitochondrial résiduel et un découplage entre la glycolyse et l’oxydation du glucose. La revascularisation peut réduire les symptômes angoreux, principalement en diminuant le déséquilibre entre besoins et apports en O₂ au niveau du muscle cardiaque. Cependant, même si la revascularisation permet d’accroître l’apport en O₂, certaines altérations du métabolisme cardiaque persistent après la revascularisation. Notamment, le muscle devient trop dépendant de l’oxydation des acides gras comme source d’énergie, principalement aux dépens de l’oxydation du glucose. Ce mécanisme accroît le découplage entre la glycolyse et l’oxydation du glucose, aboutissant à une diminution prolongée de l’efficacité cardiaque. C’est ainsi que la difficulté chez les patients angoreux vascularisés est de normaliser le mécanisme énergétique cardiaque et d’améliorer l’efficacité cardiaque. D’après des données récentes, un traitement visant à réguler le métabolisme énergétique cardiaque en diminuant l’oxydation des acides gras, ce qui augmente l’oxydation du glucose, peut permettre d’améliorer l’efficacité et la fonction cardiaques et diminuer les symptômes d’angor, même chez les patients revascularisés. Dans cet article, nous analysons les modifications métaboliques énergétiques mitochondriales cardiaques qui interviennent au niveau du cœur chez les patients angoreux et les changements apparaissant au cours de la revascularisation, ainsi que la possibilité de cibler l’oxydation des acides gras pour traiter l’angor chez les patients revascularisés ou non revascularisés.
The vascular endothelium, the surface monolayer of the vascular wall, plays an important role in the maintenance of vascular health. It releases various mediators—such as angiotensin II, endothelin-1, endothelium-derived hyperpolarizing factor, nitric oxide, prostacyclin, prostaglandin 
$H_2$, and thromboxane $A_2$—that are involved in vasodilation or vasoconstriction under specific conditions. Dysfunction of the endothelium has been implicated in various vascular pathophysiological processes, including abnormal vascular proliferation, excessive thrombus formation, vasoconstriction, and vasospasm. It is also associated with restenosis after percutaneous coronary intervention (PCI). However, there are few clinical studies on the use of pharmacological agents to improve endothelial function and decrease the rate of restenosis after PCI. Trimetazidine—an agent possessing a broad spectrum of pharmacological activities, including protection against damage to the cardiovascular system—has recently been shown to improve vascular endothelial cell function and may reduce the risk of restenosis after PCI. These actions occur through antioxidative and anti-inflammatory activities, increased adiponectin levels, and decreased insulin resistance. Although there is no direct evidence that trimetazidine can reduce cardiovascular morbidity and mortality, reductions in these may result indirectly from its effects on endothelial function. Prospective studies with a cardiovascular endpoint as a primary objective are warranted to confirm the cardioprotective effects of trimetazidine.

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die from CVDs, such as coronary heart disease, cerebrovascular disease, and peripheral artery occlusive disease. Therefore, the vascular complications of diabetes are now an important public health priority worldwide.

A 2015 statistical report on heart disease and stroke in the United States demonstrated that the number of percutaneous coronary intervention (PCI) procedures is increasing. In patients undergoing PCI, the use of drug-eluting stents (DESs) has greatly reduced the need for reintervention compared with the use of bare metal stents (BMSs). However, the incidence of in-stent restenosis in patients after PCI, using either DESs or BMSs, remains high. Thus, instantaneous restenosis continues to be a major problem after coronary stenting.

Endothelial dysfunction, a key step in the development of restenosis after PCI

Restenosis is the recurrence of narrowing of the coronary artery in a maladaptive response to damage caused by angioplasty. Chronic exposure to cardiovascular risk factors, such as high blood pressure, high blood glucose concentration, dyslipidemia, smoking, and low physical activity level impair the defense mechanisms in the vascular endothelium (Figure 1). Chronic inflammation and oxidative stress are well-known causes of endothelial dysfunction, which along with proliferation of vascular cells, production of extracellular matrix, platelet activation, and increased thrombotic activity, processes in which endothelial dysfunction has been implicated, contribute to restenosis. Many people with diabetes have increasingly complex lesion characteristics and disease comorbidities, and the risk for restenosis is high among diabetics.

The vascular endothelium—the surface monolayer of the vascular wall—plays a critical role in the maintenance of vascular health. In response to physical and chemical stimuli, it releases various vasoactive mediators, such as angiotensin II, endothelin-1, endothelial cell growth factors, endothelium-dependent hyperpolarizing factor, interleukins, plasminogen inhibitors, prostacyclin, prostaglandin H₂, nitric oxide, and thromboxane A₂.

Although the development of DESs to solve in-stent restenosis has markedly reduced the extent of restenosis after angioplasty, there is concern about delayed reendothelialization and late in-stent thrombosis. Various strategies to prevent restenosis by stimulating endothelialization or by inhibiting vascular smooth muscle cell (VSMC) proliferation have thus been tried. However, few reports have identified optimal agents with cell-specific effects on VSMCs and endothelial cells.

Role of trimetazidine in preventing the development of endothelial dysfunction and in reducing the incidence of restenosis after PCI

The piperazine derivative trimetazidine (1-[2,3,4-trimethoxybenzyl]piperazine dihydrochloride) is an anti-ischemic drug effective in treating patients with angina pectoris. Protective effects on cardiomyocytes have been shown in patients treated in primary intervention via coronary artery graft surgery. Trimetazidine’s beneficial effects on heart failure and ischemic heart disease are related to cardiac energy metabolism, which shifts from fatty acid oxidation to glucose oxidation.
tion through trimetazidine’s inhibition of mitochondrial long-chain 3-ketoacyl coenzyme A thiolase; this may contribute to its antianginal effect (Figure 3). In addition to trimetazidine’s myocardial anti-ischemic effect, it has a vasodilatory effect on coronary vessels.

We have recently shown that trimetazidine has beneficial effects on the occurrence of restenosis after vascular balloon injury in diabetes. We investigated whether trimetazidine treatment can lower the extent of restenosis occurring in the carotid artery after balloon injury in animal models of diabetes, both type 1 (streptozotocin-injected Sprague Dawley [SD] rats) and type 2 (Otsuka Long-Evans Tokushima Fatty [OLETF] rats). OLETF rats represent an obese model of type 2 diabetes, in which 5-week-old rats are allowed to grow to 24 weeks of age, at which time obesity and insulin resistance develop. Rats from both models were treated with trimetazidine at different concentrations or were sham treated with normal saline, and a well-established balloon injury procedure was carried out in the carotid artery. Two weeks after the procedure, the trimetazidine-treated rats in both models showed significantly less neointimal formation than controls; in the type 1 diabetes model, trimetazidine-treated rats also had lower mean intima-media ratios (this was dose dependent) and markedly lower in vivo cell proliferation (as measured by immunostaining for proliferating cell nuclear antigen) than controls.

A series of in vitro experimental studies have shown that reendothelialization after balloon injury is accelerated by trimetazidine treatment. In one study, trimetazidine had a direct effect on endothelial proliferation in human umbilical vein endothelial cells (HUVECs). Proliferation of HUVECs incubated in medium containing 20 μM lysophosphatidylcholine (LysoPC) was about 20% lower than in controls. Trimetazidine treatment restored cell proliferation in a concentration-dependent manner. Similarly, HUVEC proliferation was decreased by tumor necrosis factor α (TNF-α) treatment and recovered with trimetazidine treatment.

In addition, we found that trimetazidine suppresses caspase-3 activity. The effect of trimetazidine on apoptosis in HUVECs was also assessed by measuring mitochondrial membrane function. Compared with LysoPC-treated HUVECs, the number of apoptotic cells was markedly lower in the trimetazidine-treated groups. After LysoPC treatment, the ratio of active versus inactive caspase-3 was significantly higher than in controls, and trimetazidine lowered the active caspase-3 ratio in a dose-dependent manner.

These findings from in vitro cell studies and in vivo animal studies indicate that trimetazidine helps to prevent damage to the coronary vasculature and to reduce neointimal proliferation after vascular injury by way of targeting both vascular endothelial cells and VSMCs. Recent studies have shown that trimetazidine has a protective effect against restenosis after PCI in humans. In one study, trimetazidine treatment for 10 weeks lessened endothelial damage in the radial artery after transradial coronary artery angiography or transradial PCI. Another study of longer duration showed that trimetazidine treatment reduced the incidence of in-stent restenosis after PCI with DES implantation measured at the 1-year follow-up. There were also fewer major adverse cardiac events in the trimetazidine-treated group than in the control group.

Antioxidant effects of trimetazidine
There is a large amount of evidence that oxidative stress plays a role in the pathogenesis of diabetes, as well as in diabetic complications such as atherosclerosis and restenosis. Indeed, in the vascular wall, oxidative stress may be a key mechanism in processes leading to endothelial dysfunction; it promotes VSMC migration and proliferation and is...
involved in abnormal VSMC cell growth after balloon injury.\textsuperscript{2,23} We have shown that trimetazidine treatment lowers, in a dose-dependent manner, the cellular production of reactive oxygen species (ROS) in HUVECs treated with LysoPC,\textsuperscript{14} which is known to generate ROS.\textsuperscript{8} Repeated administration of trimetazidine reduces production of mitochondrial ROS in rats, and pretreatment with trimetazidine—added to cardioplegic solution—reduces oxidative damage in human patients.\textsuperscript{9,10} Also, the ischemia-induced increase in free radical production is attenuated by trimetazidine treatment before the onset of ischemia in rat hearts.\textsuperscript{24} The antioxidant effects of trimetazidine occur in various cells of the cardiovascular system.\textsuperscript{11}

**Effect of trimetazidine on the inflammatory process and on adipocytokines**

Early after endothelial denudation, an infiltration of inflammatory cells occurs in the vascular wall,\textsuperscript{25} with the presence of monocytes associated with the neointimal area.\textsuperscript{26} Neointimal thickening has been shown to be lessened with the use of anti-inflammatory agents that block the early recruitment of monocytes.\textsuperscript{27} Collectively, these findings suggest a causative role for inflammation and its associated monocyte infiltration in the development of restenosis.

Previous studies have reported that specific markers—including the adipocytokines adiponectin, monocyte chemoattractant protein-1 (MCP-1), and TNF-\textit{\textalpha}, and also the inflammatory marker high-sensitivity C-reactive protein (hsCRP)—can affect the development of restenosis and atherosclerosis.\textsuperscript{28-30} A low adiponectin concentration is a risk factor for the subsequent development of CVDs.\textsuperscript{28} MCP-1 is involved in mononuclear cell recruitment, and TNF-\textit{\textalpha} and hsCRP have important roles in the development of atherosclerosis.\textsuperscript{29,30} Trimetazidine treatment has been shown to increase adiponectin levels and decrease TNF-\textit{\textalpha} and MCP-1 levels.\textsuperscript{14} These results indicate that the protective effects of trimetazidine against restenosis occur indirectly in part through the increase in adiponectin level and decrease in proinflammatory processes and oxidative stress.

Here, I have described substantial evidence to support the concept that trimetazidine plays a positive role in reducing the extent of restenosis after PCI and have suggested some possible underlying mechanisms. However, there are several issues to note. There are differences between clinical balloon angioplasty procedures carried out on diseased vasculature in human patients and animal balloon injury models, and the carotid arteries in the balloon injury model cannot fully represent the overt atherosclerotic changes found in humans.\textsuperscript{31} In addition, in the rat model, it is VSMCs alone that contribute to the response observed after balloon injury; in humans, the injurious response in diseased vasculature arises from the interactions among several cell types, including VSMCs, endothelial cells, macrophages, and T cells.\textsuperscript{23} Furthermore, although the in vitro studies with HUVECs are performed under high-glucose conditions in an effort to mimic the hyperglycemic state in diabetics, these conditions may not be an accurate reflection of the actual state in such patients.

**Conclusion**

Trimetazidine has a broad spectrum of pharmacological activities that provide cardiovascular protection through its antioxidant and anti-inflammatory properties, enhancement of mitochondrial function, reduced fatty acid oxidation, and improved endothelial dysfunction (Figure 4). Therefore, using trimetazidine alone or in combination with other antiplatelet agents or statins may ameliorate endothelial dysfunction and improve antiatherosclerotic and anti-thrombotic efficacy. Though there is no direct evidence of a trimetazidine benefit for cardiovascular morbidity and mortality, we speculate that trimetazidine’s effect on endothelial function could affect this indirectly. Prospective studies with CVD events as a primary objective are needed to confirm these potentially beneficial effects of trimetazidine.
L’ENDOTHELÔME COMME CIBLE THÉRAPEUTIQUE CHEZ LES PATIENTS EN POST-ICP ET RÔLE DE LA TRIMÉTAZIDINE DANS LA FONCTION ENDOTHELIALE

L’endothélium vasculaire, la monocouche de surface de la paroi vasculaire, joue un rôle important dans le maintien de la santé vasculaire. Il libère différents médiateurs impliqués dans la vasodilatation ou la vasoconstriction en conditions particulières, comme l’angiotensine 2, l’endothéline-1, le facteur hyperpolarisant dérivé de l’endothélium, le dioxyde d’azote, la prostaglandine H2 et le thromboxane A2. Un dysfonctionnement de l’endothélium a été impliqué dans différents processus physiopathologiques vasculaires, y compris une prolifération vasculaire anormale, une formation excessive de thrombus, une vasoconstriction et un vasospasme. Ce dysfonctionnement s’associe aussi à une résistencée après intervention coronaire percutanée (ICP). Pourtant, les études cliniques sur l’utilisation des agents pharmacologiques pour améliorer la fonction endothéliale et diminuer le taux de resténose après ICP sont peu nombreuses. La trimétazidine, un agent au spectre d’activité pharmacologique large protégeant contre les atteintes du système cardiovasculaire, améliore la fonction cellulaire endothéliale vasculaire et réduit le risque de resténose après ICP grâce à ses propriétés antioxydantes et anti-inflammatoires, qui augmentent les taux d’adiponectine et diminuent la résistance à l’insuline. Aucune donnée directe n’indique que la trimétazidine réduit la morbidité cardiovasculaire, mais une diminution de la morbidité et de la mortalité pourrait résulter indirectement de son effet sur la fonction endothéliale. Des études prospectives ayant pour objectif principal d’évaluer la morbidité cardiovasculaire sont nécessaires pour confirmer les effets cardioprotecteurs de la trimétazidine.
In clinical practice, metabolic agents, including trimetazidine, ranolazine, and glucose-insulin-potassium, often play an adjunctive role in the treatment of angina pectoris. With the worldwide use of percutaneous coronary intervention, especially stent implantation, doctors have come to realize that some patients still suffer from angina, percutaneous coronary intervention-related complications, or poor quality of life. For such reasons, researchers have used metabolic agents to treat patients who have undergone percutaneous coronary interventions, and some progress has been observed in this area. In this review article, we mainly discuss the protective role of three widely used agents: trimetazidine, ranolazine, and glucose-insulin-potassium in patients with coronary artery disease, with a particular focus on patients who have undergone percutaneous coronary intervention. Aside from these three, there are other metabolic agents requiring further investigation to confirm their benefits for patients undergoing revascularization.

In recent years, evidence-based medicine has demonstrated that revascularization can save lives in patients with acute coronary syndrome (ACS) and improve their quality of life. Research has shown that some metabolic agents could further benefit those patients and reduce ischemia-reperfusion injury or percutaneous coronary intervention (PCI)-related injury. Metabolic agents proven to be useful in patients who undergo revascularization include trimetazidine, ranolazine, L-carnitine, glucose-insulin-potassium (GIK), ribose, dichloroacetate, and perhexiline, of which trimetazidine, ranolazine, and GIK were the most evaluated in recent years.

### Metabolic agents as adjunctive therapy in patients undergoing PCI

#### Trimetazidine

Trimetazidine, a piperazine derivative, has a long history of research, especially with regard to cardiac protection. Used worldwide as an adjunctive therapy for stable angina, trimetazidine’s protective effect in patients that undergo PCI has become a research focus.

In a small (n=20), randomized, double-blind, placebo-controlled trial, Kober et al found that trimetazidine treatment during percutaneous transluminal coronary angioplasty (PTCA) decreases intervention-related myocardial ischemia. Polonski et al reported that pretreatment with trimetazidine appears to be cardioprotective, helping to prevent myocardial ischemia during PTCA. In a study by Steg and his colleagues,
patients with acute myocardial infarction (AMI) were prescribed intravenous trimetazidine as an adjunctive therapy to primary angioplasty. The authors demonstrated that trimetazidine was safe and led to earlier resolution of ST-segment elevation. Later, in a prospective study, Labrou et al demonstrated that pretreatment with trimetazidine minimizes myocardial reperfusion injury during PCI and improves global and regional wall motion at 1 and 3 months after PCI. This result was further supported by a multicenter, randomized, and controlled study aiming to evaluate the myocardial protection of trimetazidine during PCI; the results suggested that periprocedural trimetazidine therapy can reduce the frequency of angina attacks and myocardial damage during PCI and improve left ventricular function during follow-up after PCI. A study specifically aimed at the effect of trimetazidine on recurrent angina and left ventricular structure in elderly multivessel coronary heart disease patients with diabetes mellitus after drug-eluting stent implantation also found that adjunctive therapy with trimetazidine had a beneficial effect in these patients.

For elective PCI patients, pretreatment with trimetazidine is a reasonable option; but what about acute PCI patients? To answer this question, Bonello et al carried out a study focusing on the protective effect of an acute oral loading dose of trimetazidine on myocardial injury induced by PCI. The results suggested that preprocedural acute oral trimetazidine administration significantly reduces PCI-induced myocardial injury. Aside from patients undergoing PCI, researchers also studied trimetazidine’s effect on ischemic injury and reperfusion in patients undergoing coronary artery bypass graft (CABG) surgery, with the same result.

**Cardioprotective mechanism**

A number of investigations have looked into the mechanism involved in the cardioprotection afforded by trimetazidine. Tritto et al showed us that trimetazidine protects the post-ischemic heart from neutrophil-mediated injury. In an ischemia-injury rat model, Khan et al found that trimetazidine administered at the onset of reperfusion ameliorates myocardial dysfunction and injury by activation of p38 mitogen-activated protein kinase and Akt signaling. In a recent study, Yang et al revealed that by upregulating microRNA-21 (miR-21) expression, trimetazidine counteracts the apoptotic effect of hypoxia/reperfusion. Consistent with previous studies, Senturk et al found that combination of N-acetylcysteine and trimetazidine effectively decreases oxidative stress, infarct area, and apoptotic activity in a rat model of ischemic reperfusion.

Trimetazidine also improves endothelium-dependent relaxation in patients with ischemic cardiomyopathy, owing to its antioxidant properties. A recent experimental study suggested that trimetazidine ameliorates intracellular calcium (Ca²⁺) homeostasis via a switch from lipid metabolism to glucose metabolism, thereby producing its cardioprotective effect and reducing damage to hypoxic cardiomyocytes.

On the basis of these findings, Kim et al analyzed data from the Korean Acute Myocardial Infarction Registry and found that trimetazidine improves clinical outcomes in AMI patients by significantly reducing all-cause mortality and major adverse cardiac events (MACEs) over 12 months. For specific patients, such as diabetic patients with renal dysfunction undergoing elective PCI, a study demonstrated that trimetazidine administered before elective PCI decreases the incidence of contrast-induced nephropathy (CIN).

Our team also demonstrated that long-term treatment with trimetazidine after stent implantation reduced in-stent restenosis and MACE in a 1-year follow-up study. In this study, 768 patients were enrolled and randomized into a trimetazidine group (n=384) or a control group. After drug-eluting stent implantation, all patients were treated with regular medication.

In the trimetazidine group, 20 mg trimetazidine was administered three times a day for at least 30 days. All patients received follow-up angiography 9-13 months after discharge. The final analysis included 635 patients (trimetazidine group, n=312; control group, n=323). Stent restenosis occurred in 49 (7.7%) patients. The trimetazidine group had a lower incidence of stent restenosis than the control group (4.2% vs 11.1%; P=0.001). At the 30-day follow-up, the trimetazidine group exhibited a higher left ventricular ejection fraction than the control group (65.4±10.7 vs 63.1±10.4; P=0.006). The incidence of major adverse cardiac and cerebrovascular events (MACCEs) was also lower in the trimetazidine group at the 1-year follow-up (6.1% vs 10.8%; P=0.032). Further multivariate analysis revealed that trimetazidine treatment was a predictor for stent restenosis (odds ratio, 0.376; 95% confidence interval, 0.196-0.721; P=0.003). This result was also supported by a Sprague-Dawley rat model experiment that demonstrated that trimetazidine inhibits the proliferation and migration of vascular smooth muscle cells and promotes the proliferation of human umbilical vein endothelial cells.
Aside from these benefits for the heart, trimetazidine also protects the artery from PCI-related injury. Yoon et al reported that trimetazidine effectively accelerates re-endothelialization after carotid balloon injury. Recent studies have also demonstrated that trimetazidine significantly lessens endothelial dysfunction in the radial artery after catheterization. In a recent meta-analysis, the authors concluded from nine studies involving a total of 778 patients that adjunctive therapy with trimetazidine in patients undergoing PCI may reduce myocardial injury during the procedure and improve cardiac function.

**Other protective effects**

Besides the protective effect on the cardiovascular system, recent studies suggest that trimetazidine may have potential for use in prevention of CIN. In one meta-analysis including three randomized controlled trials in the final analysis, the addition of trimetazidine treatment significantly decreased the incidence of CIN in patients that underwent coronary angiography. The authors pointed out that care should be taken in the interpretation of this result, taking into account the small sample size.

**Final comments about trimetazidine**

Collectively, these studies provide sufficient reason to believe that for elective PCI patients, pre- or perioperative treatment with trimetazidine reduces PCI-related myocardial and vascular injury and improves heart function; and that for ACS patients, an acute oral loading dose of trimetazidine or long-term treatment with trimetazidine after stent implantation would also benefit these patients; however, the use of trimetazidine for preventing CIN is not recommended as first-line therapy and still needs to be assessed in more clinical trials.

**Ranolazine**

Ranolazine is another drug used as an adjunctive therapy for angina in symptomatic patients who are inadequately controlled with first-line antianginal therapies. Among diabetic patients that have chronic angina despite treatment with up to two agents, ranolazine was found to reduce angina and sublingual nitroglycerin use and to be well tolerated. A systematic review of randomized controlled trials included seven studies and concluded that ranolazine reduces anginal symptoms among patients with symptomatic chronic stable angina pectoris and is probably cost effective.

Recent studies have shown additional benefits of ranolazine in patients with coronary heart disease. Some experimental studies have demonstrated that ranolazine reduces myocardial infarct size and improves left ventricular function. It also markedly reduces ventricular arrhythmias induced by ischemia and ischemia-reperfusion, indicating a protective role in PCI in patients with ACS. Possible mechanisms involved in these phenomena include reduction in Ca overload and oxidative stress and improvement in mitochondrial integrity. On the basis of these findings, some clinical research focused on the role of ranolazine in post-revascularization atrial fibrillation (POAF). Tagarakis et al found a protective role for oral ranolazine when administered preoperatively at a moderate dose in patients undergoing on-pump CABG surgery. Their findings suggest that perioperative treatment with ranolazine effectively reduces the incidence of POAF, a result that has been supported by further studies. In patients that underwent PCI, ranolazine has been found to reduce recurrent ischemic events and improve quality of life.

However, as presented at the 2015 American Heart Association (AHA) Scientific Sessions, the RIVER-PCI study (Ranolazine for Incomplete Vessel Revascularization) showed no incremental benefit in angina or quality of life measures from adding ranolazine treatment in an angiographically-identified population. Furthermore, an overall analysis of this study revealed that ranolazine did not reduce the composite rate of ischemia-driven revascularization or hospitalization without revascularization in patients with a history of chronic angina who had incomplete revascularization after PCI.

**Final comments about ranolazine**

In our opinion, despite a confirmed role for ranolazine in angina frequency and in quality of life, further investigation—well-designed clinical trials, especially—are warranted to evaluate its effect in CAD patients undergoing PCI. The use of ranolazine in patients that are to undergo PCI should not be encouraged for now.

**Glucose-insulin-potassium**

GIK has been used as metabolic therapy in practice for many years. Earlier studies found that GIK improves hemodynamic performance and is associated with reduced troponin I release after on-pump CABG surgery. It also improves myocardial perfusion after revascularization and lessens the LV remodeling observed at follow-up. These results are supported by other experimental research. However, a 1-year follow-up study found that GIK therapy offers no clinical benefit in patients with ST-elevated myocardial infarction (STEMI) without signs of heart failure. Further meta-analysis also suggested that GIK does not reduce mortality in patients with AMI. Despite these negative results, some important studies were carried out to determine the effect of GIK on patients with CAD. In the IMMEDIATE randomized controlled trial (Immediate Myocardial Metabolic Enhancement During Initial Assessment and Treatment in Emergency Care), Selker et al found that in patients with suspected ACS, out-of-hospital treatment with GIK did not reduce progression to MI and although it did not improve 30-day survival, it was associated with lower rates of the composite outcome comprising cardiac arrest and in-hospital mortality. Similar results were found in a 1-year follow-up of this study, whereas in those with STEMI, the composite of cardiac arrest or 1-year mortality, and of cardiac arrest, mortality, or hospitalization for heart failure within 1 year, were significantly reduced. This benefit...
might be limited to AMI patients. A further meta-analysis also revealed that administration of GIK in ACS patients did not significantly reduce mortality after the onset of symptoms.

**Final comments about GIK**

On the basis of the above, we believe that presently we do not have enough evidence to support the first-line use of GIK in patients undergoing PCI. Studies to further investigate the role of GIK in these patients are needed.

**Other metabolic agents**

L-carnitine is another adjunctive therapy for angina pectoris and has been shown to attenuate left ventricular dilation during the first year after an AMI, resulting in smaller left ventricular volumes at follow-up. In the stent era, L-carnitine has also been used in patients undergoing PCI, with inconsistent results. Xue et al found that L-carnitine as an adjunctive therapy to PCI was associated with a reduced level of cardiac markers in patients with non-STEMI. A later systematic review and meta-analysis found that, compared with placebo or control, L-carnitine was associated with a 27% reduction in all-cause mortality, a 65% reduction in ventricular arrhythmias, and a 40% reduction in anginal symptoms in patients experiencing an AMI. However, these findings were not consistent with results from another meta-analysis in which the authors concluded that there was no significant marginal benefit in terms of all-cause mortality, heart failure, unstable angina, or myocardial reinfarction in the setting of AMI for oral L-carnitine maintenance doses of 2 g or greater per day. A possible reason behind the differing results of these two studies may involve the different number of trials included in the meta-analyses (13 vs 5 respectively). On the basis of these inconsistent findings, we suggest that clinical trials—well-designed randomized controlled trials, especially—are needed to further determine the effect of L-carnitine treatment in patients with CAD, especially those planned to undergo PCI.

Recent studies have demonstrated that the metabolic agent dichloroacetate improves cardiac contractile dysfunction after ventricular fibrillation and also prevents restenosis in preclinical animal models of vessel injury. However, until more evidence is available, care should be exercised when considering its clinical use in patients undergoing PCI.

Additional metabolic agents, such as perhexilene, ribose, and others, still need further investigation to confirm their roles in patients with CAD, especially for those undergoing PCI.

**Conclusions**

There are a number of metabolic agents widely used in adjunctive therapy for anginal pectoris. Their use in patients that have undergone PCI has been under investigation for some time, with differing levels of support available for the various agents. With regard to the agents discussed in this article, we believe a sufficient amount of evidence has accumulated in support of a protective role for trimetazidine, though its use in preventing CI-N should be further investigated. In our opinion, ranolazine, GIK, and L-carnitine, among other metabolic agents briefly touched on here, require further investigation regarding their use in patients undergoing revascularization.

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**References**


Keywords: adjunctive therapy; coronary artery disease; glucose-insulin-potassium; metabolic agent; percutaneous coronary intervention; ranolazine; trimetazidine
Currently, percutaneous coronary intervention is considered one of the key treatment strategies for the management of occlusive coronary artery disease. Even with the technical advances in percutaneous coronary intervention that have made the procedure safe, with a minimal rate of complications, myocardial revascularization procedures per se still cause myocardial or renal injuries. Lately, particular attention has been paid to such complications, including periprocedural myocardial injury and contrast-induced nephropathy. These complications can occur frequently and are associated with a worse prognosis. In this regard, the search for strategies that prevent the development of these periprocedural injuries seems very important. Results of experimental and clinical studies suggest promising potential for trimetazidine in the prevention of periprocedural myocardial and renal injuries.

Trimetazidine is an anti-ischemic metabolic modulator that has been approved worldwide for symptomatic treatment of chronic stable angina. Moreover, there is sound evidence to consider appropriate the use of this agent in patients with heart failure of ischemic etiology. In the past few years, several randomized clinical trials (RCTs) have demonstrated that therapy with trimetazidine after percutaneous coronary intervention (PCI) reduces the incidence of major adverse cardiac events, recurrent angina pectoris, and stent restenosis, and that it improves cardiac function.

At the same time, evidence continues to accumulate that myocardial revascularization procedures per se cause myocardial or renal injuries, which can be associated with worse clinical outcomes.

How effective can the use of trimetazidine be in prevention of myocardial and renal revascularization injury?

Periprocedural myocardial injury during percutaneous coronary intervention

In about one-third of patients undergoing coronary revascularization by PCI, the procedure itself causes myocardial injury (termed periprocedural myocardial injury, PMI),5,6 which has been associated with an increased rate of major adverse cardiac events, including death. How effective can trimetazidine be in preventing myocardial and renal revascularization injury?
PMI during PCI is often clinically silent; however, it can be detected if the level of serum cardiac enzymes increases above the 99th percentile upper reference limit (ULR). The Joint European Society of Cardiology (ESC)/American College of Cardiology Foundation (ACCF)/American Heart Association (AHA)/World Heart Federation (WHF) Task Force Universal Definition of Myocardial Infarction 2012 defined PMI during PCI as an elevation of cardiac troponin (cTn) level above the 99th percentile URL after PCI, assuming a normal baseline troponin value. This document also noted that in patients undergoing PCI with normal (≤99th percentile URL) baseline cTn concentrations, elevations of cTn greater than 5 x 99th percentile URL occurring within 48 hours of the procedure plus ischemic, angiographic, or imaging findings are already defined as PCI-related myocardial infarction (MI) (type 4a). The document also clarifies that when a cTn value is less than or equal to 5 x 99th percentile URL after PCI and if the cTn value was normal before PCI—or when the cTn value is greater than 5 x 99th percentile URL in the absence of ischemic, angiographic, or imaging findings—the term "myocardial injury" should be used.

Herrmann in his review classified the key factors that might determine the incidence and magnitude of PMI into three groups: patient-related, lesion-related, and procedure-related. The most frequently reported among these are older age; multivessel diffuse coronary artery disease (CAD); pre-existing renal impairment; presence of anemia; plaque burden; number of lesions; presence of bifurcation lesions; tortuosity of coronary arteries; suboptimal stenting; and multiple stents. Of course, the assessment of these factors before the intervention allows risk stratification for PMI. The most common mechanisms of myocardial injury during PCI are distal embolization and side branch occlusion; others are dissection, thrombus, no reflow/slow flow, or coronary perforation.

Several strategies to protect from PMI during PCI have been applied in clinical practice. Babu et al. have divided them into three subgroups: strategies to prevent side branch occlusion, strategies to prevent distal embolization and microvascular coagulation, and strategies of protecting the myocardium itself against PMI (cardioprotection).

Regarding prevention of side branch occlusion, the current ESC/European Association for Cardiothoracic Surgery (EACTS) Guidelines on myocardial revascularization favor stent implantation in the main vessel only, followed by provisional balloon angioplasty with or without stenting of the side branch rather than routine stenting of both vessels. Several stents, designed specifically for treatment of bifurcation lesions, have undergone extensive evaluation.

Strategies to prevent distal embolization and microvascular coagulation include administration of antiplatelet and anti-thrombotic agents, use of distal protection devices, or direct stenting of the coronary lesion without predilatation.

Strategies for protecting the myocardium against PMI are based on pharmacological and nonpharmacological interventions. Among these interventions, the most discussed ones are a high dose of statins, intra-coronary β-blocker or adenosine administration, trimetazidine, cyclosporine A, and remote ischemic preconditioning. However, the ability of some of these interventions to provide effective cardioprotection has not been confirmed in all RCTs.

**Trimetazidine for the prevention of periprocedural myocardial injury in patients undergoing coronary intervention**

The first clinical trial on this issue was the open-label, randomized, controlled, two parallel groups study trial performed by Polonski et al., in which 22 patients with one-vessel CAD received oral trimetazidine, 60 mg daily, at least 4 days before percutaneous transluminal coronary angioplasty. They found that, compared with the control group (22 patients) pretreatment with trimetazidine reduced not only angina, rhythm disturbances, and ischemic ST-T changes on the electrocardiogram during the procedure, but also demonstrated a nonsignificant trend to lower levels of cardiac troponin I (cTnI) 6 and 12 hours after the procedure.

Later, two independent groups from France and Greece received more clear evidence of the ability of trimetazidine to prevent periprocedural myocardial injury in patients undergoing coronary interventions. The single-center, prospective, randomized evaluation study of Bonello et al. included 206 stable angina patients with one-vessel CAD. Patients who underwent more than one inflation procedure during PCI were excluded from the study. Half of the patients received an acute loading dose of trimetazidine (60 mg) starting 30 min before recanalization, after which the operator was allowed to proceed with angioplasty. The main outcome of this study was the frequency and the increase in the level of cTnI after a successful PCI. cTnI levels were measured before and 6, 12, 18,
and 24 hours after PCI. It was found that there were no statistically significant differences in the frequency of cTnI levels between the trimetazidine group and the control group. However, postprocedural cTnI levels were significantly reduced in the trimetazidine group at all time points (mean [standard deviation] for control vs trimetazidine group, respectively: at 6 hours, 4.2 ng/mL [0.8] vs 1.7 ng/mL [0.2], \( P < 0.001 \); at 12 hours, 5.5 ng/mL [1.5] vs 2.3 ng/mL [0.4], \( P < 0.001 \); at 18 hours, 9 ng/mL [2.3] vs 3 ng/mL [0.5], \( P < 0.001 \); and at 24 hours, 3.2 ng/mL [1.2] vs 1 ng/mL [0.5], \( P < 0.001 \)). Moreover, the total amount of cTnI released after PCI, as assessed by the area under the curve of serial measurements, was significantly reduced in the trimetazidine group (\( P < 0.05 \)) (Figure 1).

**Figure 1.** Time course of cardiac troponin I release.

Mean circulating cardiac troponin I concentrations (error bars showing standard deviation) are indicated for control (open symbols; \( n = 130 \)) and trimetazidine (closed symbols; \( n = 136 \)) groups. The arrow indicates the time of PCI. **\( *P < 0.001 \).**

**Abbreviations:** cTnI, cardiac troponin I; PCI, percutaneous coronary intervention.


In the other trial, Labrou et al.\(^\text{25}\) included 52 patients hospitalized for acute coronary syndromes. Coronary angiography was performed in all patients, and more specifically, after 6 days of hospitalization in patients with MI. Patients who had undergone primary PCI were excluded from this study. All patients received bare metal stents; drug-eluting stents were not used in the study. In addition to conventional antianginal therapy, 27 patients received 20 mg oral trimetazidine every 8 hours, starting 15 days before PCI and continuing for 3 months after the procedure. The other 25 patients were included in the placebo group. For each patient, serum cTnI and creatine kinase-MB (CK-MB) levels were measured before PCI, then at 6, 24, and 48 hours after the procedure. Serum cTnI and CK-MB measurements were considered negative for myocardial damage when levels were lower than 0.2 ng/mL and lower than 5 ng/mL, respectively. It was observed that 24 hours after PCI, cTnI levels were higher than 1 ng/mL in 7 of 27 patients (26%) in the trimetazidine group and in 11 of 25 patients (44%) in the placebo group. Forty-eight hours after the procedure, cTnI levels remained elevated in 15% of patients receiving trimetazidine and in 32% of patients in the placebo group. Twenty-four hours after PCI, CK-MB levels were above 5 ng/mL in 22% of patients in the trimetazidine group and 40% of patients in the placebo group. The authors concluded that trimetazidine can reduce myocardial reperfusion injury during PCI. They also stressed the need for further studies with inclusion of more patients.

Xu et al.\(^\text{26}\) in a single-center, prospective, randomized, controlled study again demonstrated that trimetazidine reduced post-PCI cTnI release in patients with unstable angina pectoris. A total of 106 patients who underwent successful elective PCI and drug-eluting stent implantation were randomized to a trimetazidine group (\( n = 51 \), 60 mg trimetazidine oral loading dose 0.5-1.0 hour before PCI followed by 20 mg three times daily after PCI on top of standard therapy) or a control group (standard therapy without trimetazidine, \( n = 55 \)). cTnI level was measured before and 16-18 hours after PCI. It was found that cTnI levels after PCI were higher than before the procedure in both groups of patients (\( P < 0.01 \)). However, postprocedural cTnI levels increased from 0.02 \( \mu \)g/L (95% CI, 0.01-0.03) at baseline to 0.11 \( \mu \)g/L (95% CI, 0.07-0.13) (\( P < 0.05 \)) at 16-18 hours in the trimetazidine group, whereas in the control group, it increased from 0.02 \( \mu \)g/L (95% CI, 0.01-0.03) to 1.31 \( \mu \)g/L (95% CI, 0.44-2.31) (\( P < 0.05 \)). The proportion of patients in the trimetazidine group who showed a postprocedural cTnI level elevation of greater than 0.10 \( \mu \)g/L was lower than that in the control group (\( P < 0.01 \)).

Recently Zhang et al.\(^\text{18}\) have published a meta-analysis that covered data from 9 RCTs with a total of 778 patients having undergone PCI. It was shown that additional use of trimetazidine in the periprocedural period of PCI significantly improved left ventricular ejection fraction, reduced elevated cTnI level (relative risk [RR], 0.69; 95% confidence interval [CI], 0.48-0.99), angina attacks during PCI (odds ratio [OR], 0.16; 95% CI, 0.07-0.38), and ischemic ST-T changes on the electrocardiogram during PCI (RR, 0.76; 95% CI, 0.59-0.98).

It should be noted that this meta-analysis is in line with another meta-analysis\(^\text{37}\) that also showed a cardioprotective effect of trimetazidine in patients that underwent coronary artery bypass graft surgery. The authors of both meta-analyses have noted the superiority of trimetazidine over conventional therapy during revascularization procedures. However, the authors also emphasized that new clinical trials with large samples and rigorous designs are needed.

Several mechanisms are responsible for the prevention of ischemic reperfusion injury; one of these is the ability of trimetazidine to inhibit the opening of mitochondrial permeability transition pores, a crucial event in cardiomyocyte death after myocardial ischemia-reperfusion.\(^\text{28}\)
Contrast-induced nephropathy following percutaneous coronary intervention

Contrast-induced nephropathy (CIN) or contrast-induced acute kidney injury is a common but underdiagnosed complication of coronary diagnostic and interventional procedures that is associated with increased in-hospital morbidity and mortality, prolonged hospital stay, and raised health care costs.29–33 CIN is the third most common cause of hospital-acquired acute renal failure.34

It is known that the administration of contrast media (CM) rapidly induces intense renal vasoconstriction and subsequent reduced blood perfusion. This can lead to ischemic and hypoxic damage of the renal medulla and the production of oxygen free radicals, inducing tubular epithelial damage.35 Additional factors such as hypotension, microembolization of atheromatous debris, or bleeding complications can also be responsible for the development of CIN.36

In spite of the growing importance of this complication, there is a lack of consensus on how to define CIN. According to the most recognized definition, CIN is an absolute (≥0.5 mg/dL; ≥44 mmol/L) or relative (≥25%) increase in baseline serum creatinine (SCr) levels 48–72 hours after an exposure to iodinated CM. Generally, the incidence of CIN in individuals with normal renal function who undergo PCI is low (<3%).37 However, it rises remarkably in patients with chronic kidney disease (CKD) (up to 40% and even more).29,37 Besides pre-existing CKD, other predisposing factors for CIN are diabetes, congestive heart failure, hypotension, hypertension, preprocedure shock, recent MI, anemia, female sex, advanced age, and concomitant use of nephrotoxic agents.29,38 Procedure-related risk factors for the development of CIN include high volume of CM, as well as its high osmolarity, intra-arterial injection, and multiple CM exposures within the past 72 hours.38 There is no specific treatment for CIN after PCI—prevention remains the most effective strategy. The first step in the prevention of CIN is the identification of patients at high risk. The most commonly used scoring system is the Mehran score.39 Preventive strategies for CIN include the limitation of CM volume; use of preheated (37°C) iso-osmolar CM; pre-PCI hydration with normal saline; use of N-acetylcysteine, sodium bicarbonate, and statins; and stopping nephrotoxic drugs 48 hours before and after CM exposure.40–42 The search continues for new pharmacologic and nonpharmacologic interventions for the prevention of CIN in patients undergoing coronary diagnostic and interventional procedures.

Trimetazidine for the prevention of contrast-induced nephropathy in patients undergoing coronary interventions

Onbasil et al43 were the first to clinically evaluate the efficacy of trimetazidine in the prevention of CIN in patients with high SCr levels undergoing coronary angiography or PCI. A total of 82 patients with basal SCr levels between 1.2 and 2.5 mg/dL were enrolled in a prospective double-blind, randomized, controlled trial. Indications of the coronary interventions were acute coronary syndrome, stable angina, dilated cardiomyopathy, and preoperative assessment. Of all patients, 19 had diabetes mellitus (all of them type 2). In this study, patients were randomized into a trimetazidine group (20 mg three times daily, orally, for 72 hours starting 48 hours before the procedure) or a control group. The standard parenteral hydration protocol was applied to patients in both groups. SCr levels were measured before the procedure, 48 hours, and 7 days after the procedure. An increase in SCr level exceeding 0.5 mg/day or one-quarter of the baseline value was considered as CIN. It was found that SCr levels in the control group increased significantly 2 days after the procedure (P<0.05) and returned to the baseline values on the seventh day (Figure 2). On the other hand, they did not change significantly on the second day, and they even significantly decreased on the seventh day in the trimetazidine group (P<0.05). CIN developed in 2.5% (1/40) of patients in the trimetazidine group and in 16.6% (7/42) of patients in the control group (P<0.05).

Later, Rahman et al44 in a large prospective randomized, controlled trial again confirmed the ability of trimetazidine to prevent CIN after coronary angiogram or PCI. A total of 400 patients were enrolled in this study; in contrast to the study performed by Onbasil et al,43 patients with diabetes were excluded. Of the 400 enrolled, 200 patients were treated with trimetazidine plus hydration with normal saline and 200 patients (control group) were given hydration with normal saline only. The dose of trimetazidine was 35 mg twice daily for 96 hours starting 48 hours before the procedure. It was found that the incidence of CIN was significantly reduced by administration of trimetazidine with saline in comparison with saline alone (4% vs 14%; P<0.05).

Figure 2. Serum creatinine levels in control group and trimetazidine group.

Abbreviation: TMZ, trimetazidine.


Trimetazidine and prevention of myocardial and renal revascularization injury – Lopatin
While the two above-mentioned trials43,44 enrolled nondiabetic or a mixture of diabetic and nondiabetic patients with CKD, the study performed by Shehata45 evaluated the effect of peri-procedural administration of trimetazidine on the incidence of PCI-induced myocardial injury and CIN in high-risk patients with diabetes and mild-to-moderate renal dysfunction. The primary end point of the study was the development of CIN 72 hours after PCI. A total of 100 consecutive diabetic patients with chronic stable angina and mild-to-moderate CKD were randomized into a trimetazidine group (35 mg of agent twice daily for 72 hours starting 48 hours before the procedure) and a control group (without trimetazidine). The standard parenteral hydration protocol was applied to all included patients. Additionally, N-acetylcysteine (1200 mg) was given to patients in both groups 24 hours before and after the procedure. There was no statistically significant difference between the two groups in terms of the preliminary angiographic findings and procedural characteristics. However, postprocedural mean cTnI level was significantly higher in the control group than in the trimetazidine group (6 hours: 8±0.3 vs 16±0.2 pg/mL, \( P < 0.001 \); 12 hours: 13±0.9 vs 24±0.8 pg/mL, \( P < 0.001 \); and 24 hours: 7±0.7 vs 14±0.3 pg/mL, \( P < 0.001 \)). The SCr level in the control group significantly increased 3 days after PCI and decreased on the tenth day. On the other hand, no significant change was observed in the trimetazidine group. Mean cTnI levels as well as mean SCr levels in both study groups are graphically presented in Figures 3 and 4.

CIN was noted in 6 patients (12%) of the trimetazidine group, whereas it occurred in 14 patients (28%) of the control group (\( P < 0.05 \)). Thus, the study performed by Shehata45 was the first one to evaluate both the anti-CIN and the anti-PMI effects of trimetazidine in diabetic patients with CKD undergoing elective PCI.

Last year Nadkarni et al46 published a meta-analysis that pooled data from the three above-mentioned RCTs, which altogether included 582 patients with CKD and SCr levels ranging from 1.26 to 2 mg/dL. It was shown that in patients undergoing coronary angiography, administration of trimetazidine in conjunction with normal saline and/or oral N-acetylcysteine was associated with a significant reduction in the incidence of CIN by 11% (risk difference 0.11; 95% CI, 0.16-0.06; \( P < 0.01 \)) when compared with the control group. The number needed to treat to prevent 1 episode of CIN was 9. The authors concluded that trimetazidine could be considered a potential tool for prevention of CIN in patients with renal dysfunction. On the other hand, Nadkarni et al46 emphasized that considering the small sample size of these studies and the level of evidence being 1C, decision making about the use of trimetazidine should be individualized to each patient and each clinical context.

Recently Liu et al47 have confirmed once again the renoprotective effect of trimetazidine on CIN in patients with mild-to-moderate renal dysfunction who undergo coronary angiography or PCI. In this single-center prospective, randomized
controlled clinical trial, 132 patients with renal dysfunction undergoing coronary angiography or PCI (more than half of all patients) were divided into a control group (n=70) and a trimetazidine group (n=62). Trimetazidine was administered orally 48 hours before and 24 hours after the procedure. Standard hydration was used in all included patients.

Postoperative SCr concentration was significantly lower in the trimetazidine group than in the control group at 48 hours but not at 24 hours (P=0.026 and P=0.056, respectively), whereas postoperative cystatin C level was significantly lower in the trimetazidine group both at 24 and 48 hours than in the control group (P=0.000 and P=0.025, respectively). Trimetazidine significantly reduced the incidence of CIN (8% vs 20% in control; P=0.034). Moreover, the incidence of adverse events within 12 months of follow-up was significantly lower in the trimetazidine group than in the control group (9.6% vs 22.8%; P=0.043). The Kaplan-Meier survival curves of adverse events showed that the incidence of adverse events significantly decreased in the trimetazidine group compared with the control group (log rank P=0.035) (Figure 5). A significant correlation between the adverse events and the incidence of CIN was also noted.

Akgül et al. explain the renoprotective properties of trimetazidine against CIN by its antioxidant properties. In an experimental study, the authors showed significantly higher levels of malondialdehyde and lower levels of superoxide dismutase activity in a CM alone group than in a CM plus trimetazidine group. Moreover, histopathological analysis demonstrated a significant expansion of Bowman’s capsule, tubule epithelium degeneration, tubule epithelium necrosis, and interstitial infiltration in the CM group compared with the CM plus trimetazidine group. Interestingly, none of the histopathological scores differed significantly between the CM plus trimetazidine group and the control group (without CM).

It is important to mention that the potent antioxidant effect of trimetazidine has been demonstrated not only in myocardial and renal, but also hepatic, pulmonary, intestinal, and testicular ischemia-reperfusion injuries. This allows us to consider trimetazidine a promising agent that can prevent development of ischemia-reperfusion injuries during revascularization procedures. However, several issues are still to be clarified. First of all, it is necessary to identify the optimal duration of the pre- and post-procedural administration of trimetazidine. The question regarding the optimal dose of trimetazidine also remains open. Moreover, new studies are needed to evaluate not only the efficacy but also the safety of trimetazidine in different patient populations having undergone revascularization procedures. For example, this agent is contraindicated when creatinine clearance is below 30 mL/min. The dose of trimetazidine that will be most effective in the context of prevention of ischemia-reperfusion injury in patients with creatinine clearance of 30-60 mL/min is still to be defined as well. Large-scale studies are required to answer these questions.

References

Figure 5. Kaplan-Meier survival curve of the timing of adverse events during the follow-up period.

Abbreviation: TMZ, trimetazidine.

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Trimetazidine and prevention of myocardial and renal revascularization injury – Lopatin
Keywords: contrast-induced nephropathy; percutaneous coronary intervention; periprocedural myocardial injury; trimetazidine
COMMENT LA TRIMÉTAZIDINE PEUT-ELLE ÊTRE EFFICACE DANS LA PRÉVENTION DES LÉSIONS DE REVASCULARISATION RÉNALE ET MYOCARDIQUE ?

L'intervention coronaire percutanée est actuellement considérée comme l’un des traitements clés dans la prise en charge de la maladie coronaire occlusive. Les nouvelles techniques d’intervention coronaire percutanée l’ont rendue sûre, avec un taux minimal de complications, mais la revascularisation myocardique per se provoque encore des lésions rénales ou myocardiques. Récemment, ces complications ont fait l’objet d’une attention particulière, notamment les lésions myocardiques périprocédurales et la néphropathie aux produits de contraste. Ces complications peuvent arriver fréquemment et sont associées à un pronostic défavorable. C’est pourquoi la recherche de stratégies visant à prévenir le développement de ces lésions périprocédurales est très importante. Les résultats des études cliniques et expérimentales laissent entrevoir des résultats prometteurs pour la trimétazidine dans la prévention des lésions rénales et myocardiques périprocédurales.
Is targeting only stenosis sufficient to optimally improve angina?

**THE QUESTION**

Coronary revascularization procedures are commonly performed for the symptomatic treatment of patients with myocardial ischemia. Nevertheless, current data show that even after successful revascularization a third of angina patients still suffer from pain. Angina that recurs or persists after coronary revascularization represents a significant clinical problem and its management is particularly challenging. Therefore, this begs the question: are we doing enough by targeting stenosis only?

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Myocardial revascularization with percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG) is indicated when there is significant obstruction of coronary blood flow associated with myocardial ischemia, in order to relieve symptoms or prolong survival.

Several mechanisms may explain the persistence of angina/ischemia after a revascularization procedure, including graft or PCI failure, incomplete revascularization, and disease progression in native coronary arteries. Microvascular dysfunction may play a prominent role in the unexpected prevalence of angina after the removal of obstructions in the major coronary branches.

Graft failure and new atherosclerotic lesions

Angina may recur at any time in the first few months following apparently successful CABG surgery, and may present as stable or unstable angina. In the early postoperative period, angina is usually caused by graft closure due to a technical problem. One year after CABG, angina may occur as a result of the gradual development of graft stenosis or of the progression of new atherosclerotic lesions, either in nonby-passed vessels or distal to graft anastomosis.

After 10 years, the rate of saphenous vein graft closure is about 50%, and is associated with anatomical factors (eg, artery diameter), clinical factors (eg, male sex and aging), and risk factors for atherosclerotic cardiovascular disease. Using the internal thoracic artery reduces angina recurrence and prolongs survival.

Late recurrent angina after CABG can also result from progressive atherosclerosis in a native vessel. Studies performed before the widespread use of arterial grafting found that saphenous vein graft (SVG) disease was responsible for 80% of new angina symptoms, as opposed to new native artery disease, which was responsible for 54% of the cases. Later, an analysis from the BARI trial (Bypass Angioplasty Revascularization Investigation), which investigated the use of CABG versus PCI in patients with stable angina, showed that native coronary disease progression exceeded failed revascularization as the cause of angina after five years. Disease progression occurred in native untreated arteries in two-thirds of cases. In this study, the myocardial jeopardy score fell following initial revascularization, from 60% to 17% for PCI-treated patients compared with a reduction from 60% to 7% for CABG surgery patients \( (P<0.001) \), but rebounded after five years to 25% for PCI and 20% for surgery patients \( (P=0.01) \). Myocardial jeopardy increased between study entry and the five-year follow-up in 42% of PCI-treated patients and 51% of CABG-treated patients \( (P=0.06) \).

The MASS II trial (Medicine, Angioplasty, or Surgery Study) randomly assigned 611 patients with multivessel disease, preserved left ventricular systolic function, and stable angina to CABG, PCI, or optimal medical therapy. After only one year, 12% of the patients in the CABG group, 21% in the PCI group, and 54% in the medical therapy group had angina \( (P=0.0001) \). Furthermore, after 10 years, 64% of patients in the CABG group, 59% of patients in the PCI group, and 43% in the optimal medical therapy group \( (P<0.001) \) were angina free.

Incomplete coronary revascularization

In many patients with chronic stable angina, complete revascularization is not achieved at the time of PCI or CABG. Complete revascularization of all significantly obstructed coronary segments is the goal of CABG, and recent data has shown that complete revascularization following PCI has a positive effect on long-term clinical outcomes. However, incomplete coronary revascularization following CABG or PCI is associated with increased mortality as well as with an increased incidence of myocardial infarction, repeat revascularization, and major adverse cardiovascular or cerebrovascular events.

References

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ack in the early 1990s, when I was a cardiology fellow in Mount Sinai Hospital in New York, coronary angioplasty was a very popular treatment for treating angina in patients with coronary artery disease. However, the director of the cardiac catheterization laboratory, Dr. John Ambrose, taught us something radical at the time: patients presenting with stable and even unstable angina often have nonsignificant or no coronary stenosis during angiography. It turns out that this was a very prescient observation.

Two lines of evidence strongly suggest that targeting only coronary stenosis is NOT sufficient to optimally improve angina in patients with ischemic heart disease (IHD). First, angina actually occurs in patients in the absence of coronary stenosis. In one study of 1630 patients with typical angina, the observation of angiographically confirmed \( \geq 50\% \) stenotic coronary artery disease ranged from \( 38\%-53\% \) in men and \( 15\%-29\% \) in women over 50 years old\(^2\) —which implies that the majority of these patients do not have significant coronary obstruction. And in patients with the most dramatic manifestations of IHD, namely those with ST-elevation myocardial infarction (2251 patients) or unstable angina (2406 patients), up to \( 7\%-14\% \) of men and \( 10\%-30\% \) of women have normal coronary artery angiograms.\(^2\) Second, multiple studies show that even after successful revascularization a significant number of patients still suffer from angina. The landmark COURAGE trial (Clinical Outcomes Utilizing Revascularization and Aggressive druG Evaluation) showed that after percutaneous coronary intervention on top of optimal medical therapy, many patients remain symptomatic—\( 41\% \) at three years and \( 26\% \) at five years.\(^1\) A meta-analysis which included studies published from 1992-2007 (RITA-2 [Randomized Intervention Treatment of Angina 2], SWISS II [Swiss Interventional Study on Silent Ischemia 2], MASS II [Medicine, Angioplasty, or Surgery Study 2], and COURAGE 2007) showed that angina persists in \( 29\%-31\% \) of revascularized patients from one to five years out.\(^4\) Despite the current technical advancements in revascularization procedures, angina is still present at 12 months of follow-up in \( 29.4\% \) of percutaneous coronary intervention patients and \( 23.7\% \) of coronary artery bypass graft surgery patients.\(^5\) And in the most aggressively managed IHD patient group, those with acute coronary syndrome, residual angina at one year of follow-up is found in \( 37\% \) of those patients who received early invasive therapy.\(^6\)

Taken together, these observations suggest that coronary stenosis or obstruction is not the only causative factor of symptomatic IHD, and hence revascularization alone cannot relieve angina in all patients. Other factors such as vasospasm, microvascular disease, endothelial dysfunction, thrombosis, inflammation and even an excessive heart rate can also provoke angina. And in mind that these factors are not mutually exclusive (ie, several of them can be operating simultaneously in the same patient). Thus, guidelines for IHD management emphasize global risk assessment and recommend optimizing treatment by using renin-angiotensin system–inhibitors, statins, antithrombotic agents, \( \beta \)-blockers, and/or other heart rate–lowering agents. But whatever the etiology of angina, the end result is a metabolic derangement in the cardiomyocytes leading to an imbalance between energy production and consumption. This imbalance produces increased lactic acid levels, which then stimulate sensory nerve fibers in the myocardium and manifest as angina. Correcting these derangements requires the use of unique agents, such as trimetazidine, which shifts mitochondrial energy production from fatty acid oxidation (more oxygen consuming) to glucose oxidation (more oxygen sparing) and thus can help to restore the balance between energy supply and demand, decrease lactic acidosis, and ultimately reduce angina.

References
Traditionally, ischemic heart disease has been linked to the presence of obstructive epicardial coronary artery disease. However, extensive data have failed to show that all patients who have atherosclerotic obstructions have ischemic heart disease or, conversely, that all patients who have ischemic heart disease present with obstructive coronary atherosclerosis. Obstructive coronary artery disease has been reported in asymptomatic individuals and this is referred to as silent ischemia. In contrast, obstructive coronary artery disease is absent in patients with typical angina and in patients with positive non-invasive testing. This is more obvious in women than in men. More than half the women with stable chest pain undergoing coronary angiography do not have obstructive coronary artery disease, while this is true for only one-third of men.

In addition, large myocardial infarction registries have showed an absence of flow-limiting coronary pathology in 5%-25% of cases. This changed our view of this type of patients and the term “cardiac syndrome X” emerged to describe patients who show signs of ischemic heart disease in the absence of obstructive epicardial coronary artery disease. In these patients the pathophysiological mechanisms underlying ischemic heart disease are endothelial dysfunction and microvascular dysfunction, sometimes associated with coronary microvascular spasm and epicardial coronary artery spasm.

According to the so-called “plaque-centric” hypothesis, it was thought that removing epicardial coronary stenosis by percutaneous coronary intervention could “cure” ischemic heart disease, and therefore, angina. However, in the COURAGE trial (Clinical Outcomes Utilizing Revascularization and Aggressive drug Evaluation), only 66% of stable angina patients treated by percutaneous coronary intervention were free from angina at one year, and 74% at 5 years. The recent reports of persistent angina occurring after percutaneous coronary intervention with evidence of ischemia in the absence of residual stenosis or restenosis have showed that microvascular ischemia may coexist in patients with epicardial obstructive coronary artery disease. These findings shifted the paradigm of ischemic heart disease pathophysiology from the traditional “plaque-centric” hypothesis to a multifactorial hypothesis. This new model—which Marzilli et al called the “solar system of ischemic heart disease”—is centered around myocardial ischemia, and the “orbiting planets” are the six factors that contribute to ischemia: epicardial coronary artery obstruction, endothelial dysfunction, microvascular dysfunction, coronary spasm (microvascular and epicardial), spontaneous thrombosis and platelet aggregation, and inflammation. Since epicardial coronary artery obstruction is only one of these factors, targeting epicardial coronary stenosis —when it is present—is actually only one step in the management of ischemic heart disease. A more comprehensive approach that also includes the myocardial cell and microvascular ischemia is essential to improve patient morbidity and mortality.

References
When treating patients with chronic stable angina, clinicians should aim at reducing anginal symptoms, which will improve their patients’ exercise capacity and quality of life. The traditional approach to symptom reduction is the prescription of hemodynamic drugs such as β-blockers, calcium antagonists, and nitrates. In case of poor response to medical therapy, coronary revascularization with percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG) is often performed. The rationale for prescribing hemodynamic drugs and performing coronary revascularization as the next step in the treatment of angina is the assumption that the unique cause of angina is coronary artery stenosis.

However, numerous clinical studies have proven the shortcomings of this traditional approach. In the COURAGE trial (Clinical Outcomes Utilizing Revascularization and Aggressive drug Evaluation), 2287 patients with stable coronary artery disease were randomized to undergo PCI with optimal medical therapy (PCI group) or optimal medical therapy alone.1 Optimal medical therapy included antiplatelet agents, a statin, and hemodynamic antianginal drugs alone or in combination. Although antianginal drugs were widely prescribed, 21.1% of patients in the PCI group needed to undergo additional revascularization, and at the end of the study, only 74% of patients were free of angina. The design of the BARI 2D trial (Bypass Angioplasty Revascularization Investigation 2 diabetes), which was carried out in 2364 patients with coronary artery disease and type 2 diabetes, was similar to that of the COURAGE trial.2 In the group of patients who underwent prompt coronary revascularization (PCI or CABG), more than 90% needed antianginal drugs (β-blockers, calcium antagonists, and nitrates) alone or in combination to control their symptoms. Despite this extensive use of antianginal drugs, only 66% of patients were free from angina after 3 years of follow-up. The results of the COURAGE and BARI 2D trials indicate that targeting coronary artery stenosis only is far from sufficient to optimally improve angina.

On the other hand, myocardial ischemia in the absence of obstructive coronary disease is a marker of poor prognosis. In the WISE study (Women’s Ischemia Syndrome Evaluation), women with myocardial ischemia (seen on magnetic resonance spectroscopy) who did not have obstructive coronary disease had a similarly high rate of hospitalization for unstable angina than women with obstructive coronary disease.3 Trimetazidine, an antianginal drug that controls myocardial ischemia through intracellular metabolic changes, represents a useful alternative and can be used as add-on therapy to hemodynamic antianginal drugs. A growing body of evidence supports the antianginal efficacy of trimetazidine, alone or in combination.

The data described here point to the conclusion that the treatment of angina should focus on myocardial ischemia rather than solely on coronary artery stenosis. Accordingly, the latest ESC guidelines on the management of stable coronary artery disease have recognized the important role of metabolic agents like trimetazidine.4

References
Cardiac energy metabolism alterations are the main pathophysiological factor involved in many heart conditions, such as ischemic heart disease, where oxygen delivery is impaired by the presence of stenosis. Oxygen is required to produce enough energy to maintain cardiac function using substrates such as glucose, free fatty acids (FFAs), triglycerides, and proteins. The lack of oxygen caused by ischemic heart disease alters the metabolic pathways of individual cells. Current data show that even after successful revascularization, a third of angina patients still suffer from pain. Reasons for this include: mechanical aspects such as neointimal hyperplasia/restenosis, incomplete revascularization, atherosclerotic plaque progression, microvascular dysfunction, or coronary vasospasm. However, the diffuse nature of angina and the fact that ischemia affects the metabolism of every cardiomyocyte may perpetuate this condition.

Modifying the energy substrate supply has been proposed as a way to improve the metabolic performance of cardiomyocytes. Initially, studies that used an infusion of glucose-insulin-potassium to increase the rate of glycolysis and decrease the bioavailability of FFAs to potentiate cardiac metabolism were not conclusive in showing clinical benefit. Other drugs, such as fibrates, niacin, and nicotinic acid—which act as PPAR ligands—activate nuclear hormone receptor agonists and degradation of long-chain 3-ketoacyl CoA thiolase, and therefore inhibit β-oxidation and stimulate glucose oxidation. Meta-analyses have proven its clinical benefit in patients suffering from angina pectoris secondary to ischemic heart disease, and have suggested that it may be beneficial in patients with heart failure.

As exposed previously, we can be sure that modifying the cardiomyocytes’ metabolic machinery in patients with coronary artery disease improves ischemic symptoms further than mechanical coronary interventions alone. This knowledge opens up a broad range of possibilities for improving the quality of life of our patients. The results of the ongoing ATPCI clinical trial (efficAcy and safety of Trimetazidine in Patients with angina pectoris having been treated by percutaneous Coronary Intervention), which is currently enrolling patients with angina pectoris undergoing PCI who are then randomized to trimetazidine or placebo and treated for 2 to 4 years, are expected to further our knowledge in this area.

References

Taking into account these issues, trimetazidine appears to be the best evidence-based option to optimize metabolism in ischemic heart disease. It competitively inhibits long-chain 3-ketoacyl CoA thiolase, and therefore inhibits β-oxidation and stimulates glucose oxidation. Meta-analyses have proven its clinical benefit in patients suffering from angina pectoris secondary to ischemic heart disease, and have suggested that it may be beneficial in patients with heart failure.

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Myocardial ischemia can develop either gradually—or suddenly—with the development of acute coronary syndrome (ACS).

In both clinical scenarios the extent of myocardial ischemia is the strongest predictor of prognosis. Myocardial ischemia can be treated by (i) improving blood flow to the myocardium (revascularization), (ii) decreasing myocardial demand on blood flow (eg, with β-blockers, calcium channel blockers, and ivabradine—a drug that lowers oxygen consumption and increases blood flow to the myocardium by decreasing the heart rate), and (iii) increasing myocardial metabolic efficiency when blood supply is limited (eg, with trimetazidine, a drug that improves the efficiency of energy production in myocardial cells suffering from ischemia by shifting their metabolism from free-fatty-acid β-oxidation back to glycolysis). Nitrates fall somewhere between revascularization and the latter two “conservative” strategies, because they can enlarge coronary arteries and increase blood flow, while at the same time decreasing preload (by venous dilatation). This action, in turn, decreases oxygen consumption.

The greater the extent of myocardial ischemia, the greater the benefit of revascularization will be. Revascularization not only limits AP better than conservative therapy, but it also improves the prognosis in patients with significant stenosis located in the left main coronary artery; significant stenosis located in a proximal part of the left anterior descending artery; significant stenosis located in two or three major vessels together with systolic dysfunction of the left ventricle (ejection fraction <45%); myocardial ischemia affecting a large area (>10%); and significant stenosis located in the last patent coronary artery.1

However, about 30% patients suffer from AP after successful revascularization, which significantly impairs their quality of life.2

Post-revascularization AP occurs when:

(i) Revascularization is inappropriately indicated. The only unquestionable indication for coronary revascularization in stable patients is the presence of significant ischemia with (SAP) or without (silent ischemia) angina pectoris. Revascularization simply cannot overcome the inherent risk of complications (in-stent restenosis, periprocedural myocardial necrosis, instantaneous thrombosis, bleeding during antithrombotic treatment, potential wound infection, and many others) in patients without significant ischemia. Moreover, in patients without evidence of ischemia, chest pain may have other causes, and its recurrence after revascularization cannot be considered as treatment failure.

(ii) There is a coronary etiology. In this case, AP recurs after appropriately indicated and well-performed revascularization. This relapse can be caused by target lesion failure (in-stent restenosis, in-stent thrombosis) or the progression of a lesion that was not significant at the time of revascularization. Revascularization itself does not affect the process of atherosclerosis, which can continue unless appropriate medication is prescribed. These conditions must be treated according to the underlying causes.

(iii) AP persists despite appropriately indicated revascularization, which may be due to incomplete revascularization (another significant stenosis that has been left untreated), the presence of microvessel disease, a technical complication during PCI (peripheral embolization, untreated dissection), or “stretch” pain (probably due to extension of vessel adventitia).

Several smaller studies have suggested that the incidence of chest pain is lower after implantation of fully biodegradable stents rather than metallic stents. However, the large randomized controlled trial ABSORB 3 did not confirm this finding.3 In this trial, AP occurred in 18% of patients, both in the biodegradable and drug-eluting stent groups.

Conclusion

For every patient it is necessary to determine whether chest pain is caused by ischemia, and if it is, to what extent. Based on this information, the treatment can be properly tailored to each patient to avoid unnecessary revascularization, which would not only without any benefit, but could actually be harmful.

References

Determinants of myocardial flow

The coronary circulation is composed of the epicardial coronary arteries, which are of large caliber, and the resistance vessels, which are less than 300 µm in diameter. Whereas the epicardial vessels exert little or no flow resistance, flow resistance in the resistance vessels increases gradually as the vessel diameter decreases to less than 100 µm (eg, in arterioles). Exchange of substances between blood and tissue occurs at the capillary level.

In the myocardium, blood flow largely depends on the pressure gradient between the aortic root and the left atrium ("coronary pressure"). Under normal conditions, coronary pressure is fully maintained in the epicardial vessels, with minimal or no loss of pressure in the distal epicardial arteries. In contrast, intracoronary pressure decreases along the microvasculature to a pressure of 20-30 mm Hg (with most of the pressure dissipating in vessels with a diameter of 100-300 µm). As a result of a decrease in microvascular resistance caused by metabolic changes—possibly involving adenosine, a metabolite of adenosine monophosphate which induces vascular muscle relaxation—work-related myocardial flow increases.

The resulting flow increase is augmented by endothelium-dependent factors, and this faster flow exerts more shear stress on the endothelium, stimulates the enzyme nitric oxide synthase (eNOS), triggering the release of nitric oxide, which relaxes smooth muscles. In this scenario, endothelial cells and smooth muscle cells interact closely, which helps the vessels adjust their diameter according to changes in flow rate in the microvascular and epicardial vessels.

Coronary reserve

A good understanding of the physiology of the coronary circulation is necessary to understand the concept of coronary reserve. In a nutshell, coronary reserve refers to the ability of the vascular circuits to adapt to myocardial oxygen consumption by vasodilation. Depending on the level of endothelial health and on the extent of the mechanical obstruction present in the epicardial arteries as a result of the atherosclerotic process, an adaptive process called vascular remodeling may take place. This process initially leads to an increase in vessel diameter. When atherosclerosis involves the lumen, the percentage of obstruction will affect the coronary reserve capacity, ie, the ability to lower vascular resistance, and thus increase flow, so that the arterial blood can reach peripheral tissues without altering cellular metabolism. But this compensation mechanism is limited. Unless we try to stop the progress of atherosclerosis or remove the obstruction, with medication and/or invasive treatments such as myocardial revascularization procedures, the damage may be irreversible and permanently alter the affected vessel, and thus tissue function.

Conclusion

The mechanisms involved in the genesis of myocardial ischemia and its manifestation as angina are very complex and go beyond the epicardial arteries. Therefore, efforts aiming to normalize the lumen of the arteries or bypass the obstruction only act on part of the problem. Fortunately, we now have drugs that can improve cell metabolism, such as trimetazidine, or new drugs that can reduce the heart rate, such as ivabradine, a drug whose pleiotropic effects lead to vasodilatation and the release of nitric oxide, and thus improve endothelium function. But we should not forget all the other drugs that have been shown to have a beneficial effect on the outcome of patients with coronary heart disease, nor the positive effects of healthy eating and physical activity.

References

Microvascular angina (MVA) is found in about one-third of patients undergoing coronary angiography for angina who have no significant obstructive coronary lesions, and is strongly associated with adverse long-term prognosis.1 In patients with normal, “near-normal,” or restored epicardial flow, several factors contributing to an imbalance between oxygen demand and supply may coexist. About half the patients with coronary artery disease (CAD) have concomitant hypertension, and a growing proportion of elderly patients may present with aortic stenosis (AS). In this group of patients, increased oxygen demand is the result of increased left ventricular end-systolic pressure, left ventricular hypertrophy, impaired diastolic function, increased heart rate, and increased wall stress. As left ventricular hypertrophy progresses, coronary flow reserve may be affected by increased diastolic filling pressure, which compresses the endocardium, impairs perfusion, and reduces capillary distribution.2 In patients with AS, MVA has been attributed to preexisting abnormal resting arteriolar vasodilation in patchily distributed microvasculature preserving myocardial perfusion and abnormally constricted prearteriolar vessels preventing distal pressure overload.3

MVA may follow an endothelium-dependent or an endothelium-independent pattern. According to the current in-depth understanding of the pathways underlying angina symptoms, there is a close correlation between the ratio of oxygen demand to oxygen supply and cardiac energy metabolism (substrate utilization, production of ATP by oxidative phosphorylation, and ATP transfer and utilization).4 The cardiac metabolic system is very flexible, and can switch from one energy source to another. However, its adaptive capacity decreases in states associated with increased oxygen demand or steadily decreased coronary blood flow, triggering metabolic remodeling. Prolonged energy deficit triggers the expression of fetal genes and a switch from fat to glucose metabolism, stimulates glycogen accumulation and changes in cell signaling, increases the number of dysfunctional mitochondria, leads to collagen deposition, macrophage infiltration, fibrosis, depletion of sarcomeres, and activates apoptosis. More profound changes occur in stunned myocardium and result from inhibition of Na-K-ATPase, increased intracellular Na+ level, Ca2+ overload, stimulation of reactive oxygen species (ROS) production, and depression of contractile function in near normal coronary flow. Revascularization partially attenuates these changes, but patients may still experience coronary microembolization and microvascular obstruction, which may lead to abnormal gene expression and apoptosis.5 Apoptosis occurs in low-flow states and may be triggered by reperfusion injury and severe energy depletion and follows either intrinsic mitochondria-mediated or extrinsic membrane-mediated pathways. The intrinsic pathway involves mechanisms that impact the functioning of mitochondrial permeability transition pores (mPTPs). The extrinsic pathway is receptor-mediated and may be activated by oxidative stress late after reperfusion. Reperfusion injury and slow-reflow states contribute to necrosis, increased mitochondrial membrane permeability, cell swelling, lysis, fragmentation of cellular structures, activation of inflammatory pathways, and leukocyte infiltration.

These maladaptive cascades often partially persist after epicardial flow is restored and should be addressed medically. Metabolic agents such as trimetazidine counteract the effect of myocardial ischemia on mitochondrial membrane permeability by diminishing oxidative stress and inhibiting mPTP opening, and also reduce caspase 3 activity and apoptosis.6 The mechanisms that underlie angina are so complex that it cannot be resolved by relying on revascularization only; other nonmechanistic approaches are therefore needed to manage patients after revascularization.

References
The number of percutaneous coronary angioplasty procedures (PCI) performed in patients with chronic stable angina (CSA) has increased tremendously in the last two decades. In a series of 2000 patients with CSA (of whom 39% underwent PCI and 28% CABG) almost a third had multiple episodes of angina per week after 6 months of follow-up. Moreover, the Euro Heart Survey reports that 60% of patients with persistent angina post-PCI are moderately/severely disabled.

The most common causes of persistent/recurrent angina post-PCI are either structural ("stretch pain," in-stent restenosis, in-stent thrombosis, incomplete revascularization, or progression of coronary atherosclerosis) or functional (microvascular dysfunction or epicardial coronary spasm). A recent meta-analysis of randomized clinical trials comparing PCI versus optimal medical therapy (OMT) in patients with CSA has shown that PCI does not reduce the risk of mortality, cardiovascular death, nonfatal myocardial infarction, or revascularization procedures; however, it provides greater relief from angina compared with OMT, at least in the first year. Most international guidelines recommend revascularization procedures in CSA only when symptoms are not controlled by OMT.

In-stent restenosis usually manifests between 4 and 8 months after PCI and is associated with angina and objective evidence of myocardial ischemia on provocative testing. If OMT fails to control it, repeat revascularization is usually required. However, the use of drug-eluting stents (DESs) has substantially reduced its occurrence.

Inappropriate vasoconstriction of small vessels in the distal coronary bed of the target vessel is a frequent cause of positive stress tests after successful angioplasty. Stent implantation also induces distal coronary endothelial dysfunction. Exercise-induced spasm of a large epicardial coronary artery in the distal-post stent segment has been documented and reported. The two most frequent causes of early post-CABG angina are anastomotic site lesions and rapid venous graft degeneration/thrombosis. A thorough clinical evaluation is crucial in such patients. In those with established angina, direct coronary angiography should be performed, while non-invasive stress tests (vs myocardial scintigraphy/stress echocardiography) are appropriate in those whose probability of having angina is intermediate. Estimation of coronary flow reserve is a boon for those in whom angiography shows borderline stenosis (≤70%). A fractional flow reserve (FFR) of 0.75 or less is usually considered to be a good indication for PCI. The DEFER trial has shown that performing PCI for lesions with an FFR of 0.75 or more does not improve symptoms nor prognosis.

Achieving and maintaining an optimal body weight and following a graded exercise training program are known to improve exercise capacity in patients with CSA. Achieving an optimal hematocrit and excellent blood pressure control, and lowering LDL-C levels to below 70 mg/dL are all extremely important ways to improve the prognosis of these patients. Post-PCI stretch pain is usually treated with analgesics and is, thankfully, self-limiting. The functional causes of recurrent angina (microvascular dysfunction/epicardial coronary spasm) respond best to diltiazem and long-acting nitrates. Trimetazidine (an inhibitor of fatty acid oxidation), which improves angina by shifting myocardial metabolism toward glucose oxidation (TRIMPOL II study) has also been found to be useful in such patients. β-Blockers should be prescribed to all post-PCI patients unless contraindicated. Statins and angiotensin-converting enzyme (ACE) inhibitors should also be part of OMT in most patients. High compliance rates with OMT, such as those obtained in the COURAGE trial, (90% at 5 years) are not easy to obtain in clinical practice unless combinations are used to reduce the number of pills patients are prescribed. Thankfully in India various combinations are freely available. Recently, the BEAUTIFUL and ASSOCIATE trials have shown some promising results for the use of ivabradine as an add-on therapy or in those in whom β-blockers are contraindicated to reduce the frequency of angina attacks and the number of cardiac events.

References
Despite the progress made by the various therapeutic methods used in cardiology in the last decades, coronary artery disease remains the leading cause of mortality and morbidity worldwide. Percutaneous coronary intervention is an effective and safe treatment to relieve severe stenosis in patients with coronary artery disease, but studies have shown that many patients still suffer from recurrent angina or silent myocardial ischemia after revascularization.1

Traditional antianginal agents for the treatment of stable angina pectoris include nitrates, calcium antagonists, and β-blockers, which reduce angina attacks either by reducing ATP consumption via a reduction in the heart rate and blood pressure or by increasing ATP production through an increase in coronary blood flow.2 Optimizing myocardial metabolism with metabolic agents is a new strategy that can be used in patients with stenotic coronary artery disease. These drugs represent a new class in the treatment of ischemic heart disease. Trimetazidine is a metabolic agent, and unlike conventional antianginal drugs, it restores the balance between myocardial oxygen supply and demand by selectively inhibiting the long-chain 3-ketoacyl coenzyme A thiolase, thus partially suppressing the β-oxidation of fatty acids, stimulating glucose metabolism, and increasing myocardial ischemic tolerance.3,4 Xu et al5 have showed that adjunctive therapy with trimetazidine after drug-eluting stent implantation reduces the incidence and the severity of angina pectoris as well as that of silent ischema in elderly patients with multivessel coronary artery disease and diabetes mellitus. In addition, pretreatment or concomitant treatment with trimetazidine seems to have a cardio-protective effect in patients undergoing percutaneous coronary intervention. These studies have shown that trimetazidine treatment results in an improvement in several ischemic parameters, such as a reduction in the frequency of angina pectoris attacks and of myocardial damage during percutaneous coronary intervention and coronary artery bypass graft surgery. These benefits are achieved because trimetazidine protects the heart from ischemic damage and oxidative stress. In addition, trimetazidine has also been shown to improve left ventricular function in the follow-up period after percutaneous angioplasty.6

References

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Ischemic heart disease is a diffuse disease encompassing not only the epicardial compartment, but also the microvascular compartment. This is one of the reasons for continuing chest pain even after complete mechanical epicardial revascularization: about 40% of all bypassed or stented patients still have angina one year after the procedure. We present a case in which the patient had residual ischemia despite complete revascularization with the use of fast-generation drug-eluting stents. In cases such as this one—in which further revascularization is impossible—a metabolic drug that can reduce ischemia may improve symptoms.

A fifty-two year-old male smoker, with a history of hypertension and dyslipidemia, was admitted to our clinic with stable angina triggered by low-level physical activity, which he had started to experience approximately one year earlier (class III CCS). His ECG at rest was normal, and did not show any signs of ischemia. Echocardiography did not show any kinetic dysfunction at rest; the ejection fraction was 53%, the left ventricle was not dilated, and there were no significant valvular lesions. In addition, the cardiac markers of myocardial necrosis were normal.

Coronary angiography, which was performed through right radial access, showed 80% stenosis in the distal left main (LM) artery. There was 70% stenosis in the proximal and middle segments of the left anterior descending (LAD) artery, where there were two Medina 110 bifurcation stenotic lesions in the first and second diagonal branches, respectively. The SYNTAX score was 28. According to the ESC Guidelines for Myocardial Revascularization, the patient had left main artery disease with a SYNTAX score of 23-32, which corresponds to class I and level of evidence B for coronary artery bypass graft surgery (CABG). Treatment with percutaneous coronary intervention is class IIIa with a level B of evidence. However, the Heart Team decided that percutaneous coronary intervention was an option as the patient was reluctant to go through CABG surgery.

Before the procedure, the patient was preloaded with clopidogrel 600 mg and 500 mg aspirin. The procedure was performed through radial access, and a JL 4, 6F guiding catheter was used to canulate the LM. Two wires were placed in the LAD and LCX. First, we predilated the LM-LAD with a balloon, after which two overlapping stents (Biofreedom 3.0x28 mm and 3.5x24 mm) were implanted into the LAD. There was no significant stenosis in the diagonal ostia (grade III TIMI flow). Another overlapping stent was placed in the LM and ostioproximal part of the LAD (Biofreedom 3.5x24 mm). We then dilated the stented region (LM and LAD) with noncompliant (NC) balloons. Because there was 70% stenosis in the LCX ostium we performed a balloon dilation of the LAD and LCX ostia. The final angiographic result showed no dissection and no residual stenosis, and normal flow was restored in all treated vessels. A final intravascular ultrasound (IVUS) was performed in the LAD, LCX and left main artery, and showed no signs of dissection and stent strut malposition. The circumflex artery ostium was not compromised, so there was no need for additional stenting. The patient was discharged 2 days after the procedure; he had no angina symptoms, nor any elevation of the markers of myocardial necrosis, and there were no adverse events. He was prescribed rosuvastatin, ramipril, bisoprolol, clopidogrel, and acetylsalicylic acid.

At 1 month of follow-up, there were no adverse events, but the patient still had intermittent episodes of chest pain. The stress test at 11 METs (metabolic equivalents) was ECG negative, with slight chest discomfort. For this reason we decided to add trimetazidine to his treatment. At the next visit—the following month—the patient was completely asymptomatic. This case clearly illustrates the fact that even after complete mechanical revascularization microvascular dysfunction can still cause discomfort. Increasing hemodynamic therapy provides no additional benefit in this kind of situation and the only option is to directly alter the ischemic threshold by adding a metabolic drug (eg, trimetazidine) according to the currently proposed algorithm for the treatment of angina.3

References
Angina is now recognized as a multifaceted disease where coronary artery obstructions are only one among many contributing factors. Because of its central involvement in a number of ischemic processes, the cardiac cell is recognized as a major player in cardiac ischemia. At the cell level, myocardial ischemia is characterized by altered myocardial energy metabolism, which results in an ionic imbalance, misuse of and deficit in energy, and ultimately functional defects. During ischemia, trimetazidine acts directly at the cell level by decreasing fatty acid oxidation and increasing glucose oxidation, which helps restore normal energy metabolism. This leads to an overall improvement in the general function of the cell and, at the organ level, provides anti-ischemic activity. By directly targeting the cardiac cell, trimetazidine’s mechanism of action complements those of hemodynamically active antianginal therapies, thus maximizing clinical efficacy when used in a combination strategy. Trimetazidine has been shown to provide additional reduction in symptoms and increase exercise capacity in angina patients whose symptoms are inadequately controlled by β-blockers and/or calcium channel blockers. The beneficial effect of trimetazidine has been demonstrated in various angina patients, including those with a history of myocardial infarction, previous percutaneous coronary intervention, diabetes, or left ventricular dysfunction. In addition to its proven antianginal effect, trimetazidine may also provide extra benefits in terms of cardioprotection and prognosis in many cardiovascular patients.

Stable angina pectoris, a clinical manifestation of myocardial ischemia, is a chronic disease associated with poor prognosis and impaired quality of life. Patients with severe angina are at greater risk for cardiovascular events, including myocardial infarction or death, and the rate of hospitalizations is particularly high in this population.

One therapeutic option for relieving angina symptoms is the use of invasive procedures, such as myocardial revascularization. However, this type of approach has unclear effects on survival, and its use is restricted to angina patients with obstructive coronary artery stenosis. Thus, medical therapy—by reducing the symptoms of angina, increasing exercise tolerance, and improving quality of life—remains a cornerstone in the management of angina patients. Antianginal drugs exert their effects by reducing cardiac workload, i.e., reducing myocardial oxygen consumption...
and/or increasing oxygen supply to the heart. This is the mode of action of standard antianginal treatments, such as β-blockers or calcium channel blockers. Another approach consists in optimizing oxygen use by directly increasing energy production at the cardiac level, such as with the anti-anginal agent trimetazidine. In view of their complementary mechanisms of action, antianginal drugs are often used in combination for additive or synergic effects. Here we review the pharmacological rationale and clinical efficacy of trimetazidine in patients with stable angina pectoris, in light of recent experimental and clinical findings.

**Angina: a single clinical entity with multiple etiologies**

Angina pectoris is generally recognized as the clinical expression of underlying coronary artery disease (CAD). In patients with CAD, myocardial ischemia results from flow-limiting obstructions in the epicardial coronary arteries, as documented by coronary angiography. However, a significant proportion of patients with typical angina symptoms do not present obstructive lesions in their angiograms. In a recent report, 83.5% of angina patients with no previously documented CAD had no evidence of obstructive CAD. These patients often present with occult coronary abnormalities, which explain their angina symptoms. These vascular defects often occur concomitantly, supporting the notion that multiple causative mechanisms in angina—including endothelial dysfunction, microvascular impairment, and myocardial bridging—are common. Beyond coronary mechanisms, additional nonvascular mechanisms can contribute to myocardial ischemia (Table I). These are particularly relevant in a significant minority of angina patients for whom there is no coronary explanation for their symptoms. Because of its central involvement in a number of ischemic processes, including inflammation and impaired myocardial energy metabolism, the cardiac cell is recognized as a major nonvascular player in ischemic heart disease (Table I). Progression in angina is a complex and multifactorial process, with both vascular and nonvascular contributing mechanisms. Coronary obstruction represents only one piece of the puzzle.

### Targeting the cardiac cell for increased clinical efficacy

The recognition of 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 cell. One option would be to adjust treatment for each patient according to the underlying causes of angina. However, this would prove difficult to diagnose in practice. A more convenient approach would consist in a global therapeutic strategy that encompasses all causes of ischemia. In the Euro Heart Survey, over half of stable angina patients (59%) were prescribed two or more antianginal drugs. Combining different anti-ischemic drugs, each with its own distinct mechanism of action, may improve clinical efficacy by additive or even synergic effects. Moreover, a combination strategy allows more treatment flexibility, by permitting drug selection according to a patient’s comorbidities and/or cardiac function.

### Table I. Multiple causes of stable ischemic heart disease.

These different mechanisms of ischemia are not mutually exclusive and often occur concomitantly during angina.

<table>
<thead>
<tr>
<th>Origin</th>
<th>Possible mechanisms of ischemia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vascular</strong></td>
<td>Flow-limiting stenosis (atherosclerosis)</td>
</tr>
<tr>
<td>Macrovessels</td>
<td>Endothelial dysfunction</td>
</tr>
<tr>
<td>Microvessels</td>
<td>Vasospasm</td>
</tr>
<tr>
<td>Cardiomyocytes</td>
<td>Muscle bridge</td>
</tr>
<tr>
<td>Microemboli</td>
<td>Inflammation</td>
</tr>
<tr>
<td><strong>Nonvascular</strong></td>
<td>Impaired energy metabolism</td>
</tr>
<tr>
<td>Cardiomyocytes</td>
<td>Defective cellular oxygen transport</td>
</tr>
<tr>
<td></td>
<td>Mitochondrial dysfunction</td>
</tr>
<tr>
<td></td>
<td>Inflammation/fibrosis</td>
</tr>
</tbody>
</table>

### Selected Abbreviations and Acronyms

- **ATP**: adenosine triphosphate
- **ATPCI**: efficAcy and safety of Trimetazidine in Patients with angina pectoris having been treated by percutaneous Coronary Intervention
- **CAD**: coronary artery disease
- **DIETRIC**: estudio prospectivo en pacientes Diabéticos de la Efectividad y tolerabilidad de la Trimetazidina en asociación al tratamiento previo de su enfermedad Coronaria
- **MACCE**: major adverse cardiac and cerebrovascular event
- **METRO**: ManagEment of angina: a reTRospective cOhort
- **PCI**: percutaneous coronary intervention
- **TRIMPOL**: TRIMetazidin in POLand

The heart requires a large amount of energy to support its continuous contractile activity, making energy metabolism a fundamental process in the cardiac cell. Under normal conditions, the main source of energy in the cardiac cell comes from the oxidative metabolism of fatty acids in the mitochondria, which provides 70% of total adenosine triphosphate (ATP). However, the mitochondrial oxidation of glucose remains a more efficient metabolic process, as it requires 12% less oxygen than fatty acids for an equivalent ATP production. During ischemia, where oxygen supply is limited, oxidative metabolism is dramatically reduced, and glycolysis (ie, conversion of glucose to pyruvate) becomes a preponderant process.
source of energy (Figure 1). This alteration in myocardial metabolism is accompanied by an uncoupling of glycolysis and glucose oxidation, an increase in intracellular lactate and protons, and an ionic imbalance, with serious consequences at the cellular level. These maladaptive metabolic changes cause a depletion in the cellular energy store, as evidenced by a decrease in ATP production and other high-energy phosphate levels. In order to maintain ionic homeostasis, ATP-dependent ion transporters are activated to eject protons and sodium out of the cardiac cell. This consumption of ATP for noncontractile purposes further impairs cardiac function, in a context where energy levels are already dramatically reduced. This vicious cycle has been summarized by Pepine et al in the following terms: “ischemia begets more ischemia”.

Trimetazidine acts directly at the cell level by inhibiting long-chain 3-ketoacyl coenzyme A thiolase, a mitochondrial enzyme involved in fatty acid oxidation. Inhibition of this enzyme leads to a decrease in fatty acid oxidation and, as a consequence, stimulates glucose oxidation and inhibits glycolysis (Figure 1). This beneficial effect of trimetazidine on energy metabolism pathways is accompanied by a restoration of intracellular energy levels. This has been demonstrated in animal studies and confirmed in a clinical setting, where treatment with trimetazidine for 3 months was shown to increase myocardial levels of high energy phosphates in heart failure patients by 33%. This overall improvement in ATP production with trimetazidine protects the cell against acidosis and ionic imbalance during ischemia. Notably, trimetazidine has been shown to prevent calcium overload, the production of free radicals, and apoptosis in the cardiac cell during reperfusion. By preventing all these deleterious effects, trimetazidine maintains the contractile function of the cardiac cell and reduces anginal symptoms.

To summarize, trimetazidine exerts its anti-ischemic effects directly at the cardiac cell level, by optimizing ATP use and opposing deleterious changes that occur during ischemia.

Clinical efficacy of trimetazidine in stable angina

The anti-ischemic and antianginal efficacy of trimetazidine has been demonstrated in a range of randomized clinical trials involving nearly 4000 patients with chronic stable angina worldwide. This clinical efficacy is associated with a good safety profile. The positive benefit-risk balance of trimetazidine in stable angina was recently reaffirmed in an assessment of the European Medicines Agency in 2012 and recognized in the latest European Society of Cardiology guidelines for the treatment of stable CAD in 2013, and for the treatment of heart failure in 2016.

◆ Efficacy of trimetazidine in comparison with β-blockers

The antianginal efficacy of trimetazidine (60 mg daily) was compared with that of propranolol (120 mg daily) in a randomized, double-blind, multicenter study in 149 patients with stable angina and documented CAD. Results indicated that the antianginal efficacy of trimetazidine was similar to that of the β-blocker. The improvement in clinical parameters was comparable in both groups of patients after 3 months of treatment (mean propranolol-trimetazidine difference in number of weekly angina attacks, –2.0 \([P=0.117]\); and in weekly use of short-acting nitrates, –1.1 \([P=0.426]\)). A similar anti-ischemic effect for trimetazidine and propranolol was observed during exercise testing.

Figure 1. The alteration in fatty acid oxidation during cardiac ischemia is accompanied by an increase in glycolysis and a decrease in glucose oxidation, with deleterious consequences for cardiac homeostasis and efficiency (black arrows). The inhibition of fatty acid oxidation with trimetazidine restores the coupling of glycolysis to glucose oxidation, which in turn increases production of ATP and restores cell function (red arrows). Modified after reference 8: Fillmore et al. Br J Pharmacol. 2014; 171:2080-2090. © 2014, The British Pharmacological Society.
This study shows that trimetazidine possesses the clinical efficacy of a first-line antianginal agent. The comparable efficacy of trimetazidine and \(\beta\)-blocker was acknowledged in the 2013 European Society of Cardiology guidelines on the management of stable CAD.\(^{22}\)

**Efficacy of trimetazidine in comparison with calcium channel blockers**

The antianginal efficacy of trimetazidine (60 mg daily) was compared with that of nifedipine (40 mg daily) in a randomized, double-blind study with a cross-over design in 39 patients with stable angina and documented CAD.\(^{25}\) Each treatment lasted for 6 weeks, separated by a 1-week washout period. Both treatments reduced the frequency of angina attacks to a similar degree. The comparable anti-ischemic activity of the two drugs was also shown by a similar improvement in exercise test parameters (ie, increase in total workload of 24% and 30% for trimetazidine and nifedipine, respectively; in duration of exercise of 13% and 17%; and in time to 1-mm ST-segment depression of 17% and 19% [with no significant difference between treatments]).

In a separate study using a parallel-arm design, trimetazidine and the nondihydropyridine calcium channel blocker diltiazem decreased the number of weekly angina attacks and nitrate consumption to the same extent. Moreover, both drugs had a similar effect profile with regards to exercise test parameters.\(^{26}\) These clinical data suggest that trimetazidine could be an effective alternative to calcium channel blockers in the treatment of stable angina patients.

**Efficacy of trimetazidine as a combination therapy with \(\beta\)-blockers**

The antianginal efficacy of trimetazidine as an add-on therapy to \(\beta\)-blockers was evaluated in a series of randomized clinical studies.\(^{27-29}\) In the TRIMPOL-II (TRIMetazidine in PO-Land-II) study, a total of 426 stable angina patients with documented CAD were randomized to trimetazidine (60 mg daily) or placebo, in addition to receiving a background treatment of metoprolol (100 mg daily).\(^{30}\) Exercise testing, evaluated at baseline and after 3 months of treatment, revealed a significant improvement in the trimetazidine-treated group compared with the placebo group (increase in total exercise duration of 16% and 10% for trimetazidine and placebo, respectively; in total workload of 14% and 7%; in time to onset of angina of 24% and 13%; and in time to 1-mm ST-segment depression of 29% and 22% \([P<0.01\) for all]). Clinical symptoms (number of angina attacks, use of nitrate, and intensity of anginal pain) were also significantly reduced with trimetazidine plus metoprolol compared with placebo plus metoprolol.

In a separate randomized, double-blind study, the antianginal efficacy of trimetazidine in combination with propranolol was evaluated versus isosorbide dinitrate plus propranolol.\(^{31}\) Stable angina patients (N=53) for whom symptoms were not adequately controlled by propranolol (120 mg daily) received add-on therapy with trimetazidine (60 mg daily) or isosorbide dinitrate (30 mg daily) for 2 months. Patients who received trimetazidine had a greater reduction in the weekly number of angina attacks (Figure 2) and in consumption of short-acting nitrates compared with the reference group. Moreover, exercise test results only improved in the group where trimetazidine was used (increase in exercise duration of 14% versus 2% for trimetazidine versus isosorbide dinitrate, respectively; and in time to 1-mm ST-segment depression of 15% versus 3%). Overall, trimetazidine appeared to have better antianginal efficacy compared with the long-acting nitrate isosorbide dinitrate.

The use of trimetazidine in combination with a \(\beta\)-blocker provides better clinical efficacy than \(\beta\)-blocker alone or another combination strategy. This may be related to an additive, or possibly synergistic, effect of the two drugs, each of which works via a distinct mechanism of action. The use of trimetazidine, which acts directly at the cardiac level, appears a rational choice for optimizing the treatment of patients inadequately controlled by \(\beta\)-blockers.

**Antianginal effectiveness of trimetazidine in different clinical situations**

**In everyday practice**

The antianginal effectiveness of trimetazidine in clinical practice was evaluated in a large prospective cohort of 1213 outpatients with stable angina inadequately controlled by standard therapy consisting of \(\beta\)-blocker alone or a combination of \(\beta\)-blocker plus long-acting nitrate or calcium channel block-
All patients received trimetazidine (35 mg modified-release formulation, twice daily) on top of their standard treatment for 2 months. In all patients, trimetazidine significantly reduced the number of weekly angina attacks, regardless of the background therapy (Figure 3). Moreover, in this study maximal antianginal efficacy was achieved with a dual combination of trimetazidine and β-blocker only. These data suggest that combination therapy with β-blocker and trimetazidine should be considered for the optimal management of stable angina patients in real-life situations.

![Figure 3. Mean number of weekly angina attacks in outpatients whose symptoms were inadequately controlled by standard therapy (β-blocker alone, β-blocker + long-acting nitrate, or β-blocker + calcium channel blocker) before (gray bars) and after (red bars) add-on treatment with trimetazidine for 2 months. Data are presented in patients who had ≥7 angina attacks per week at inclusion. Modified after reference 32: Nesukay. Ukr J Cardiol. 2014;2:43-47. © 2014, Ukrcardio.](image)

### In angina patients with diabetes

Angina patients often present with associated comorbidities that make their therapeutic management particularly challenging. Patients with concomitant diabetes mellitus and CAD are considered to be at especially high cardiovascular risk. In fact, type 2 diabetes patients without previous myocardial infarction have a similar risk of myocardial infarction to that of nondiabetic patients with previous myocardial infarction. In diabetic patients, cardiac energy metabolism is significantly altered, and these alterations are further amplified in the presence of underlying ischemic heart disease. Trimetazidine appears an attractive tool for the management of angina patients with diabetes. This hypothesis is supported by findings from the DIETRIC trial (estudio prospectivo en pacientes Diabéticos de la Efectividad y tolerabilidad de la Trimetazidina en asociación al tratamiento previo de su enfermedad Coronaria), a prospective, observational study that investigated the antianginal effect of trimetazidine in 580 outpatients with type 2 diabetes and CAD. The addition of trimetazidine (60 mg/day) to conventional background therapy for 6 months decreased the number of angina episodes in clinical practice (from 2.8/week at baseline to 0.9/week after treatment \(P<0.001\)). Short-acting nitrate consumption was also reduced (from 2.5/week at baseline to 0.7/week after treatment \(P<0.001\)). Interestingly, in a separate study in the same population (diabetic patients with CAD), the addition of trimetazidine on top of standard treatment was able to reduce not only symptomatic episodes of myocardial ischemia, but also silent ischemia, a feature commonly observed in diabetic patients and associated with a worse prognosis.

Trimetazidine has also been demonstrated to have benefits in challenging clinical situations, such as in elderly diabetic patients with multivessel coronary heart disease undergoing percutaneous coronary intervention (PCI). In this population (N=700), treatment with trimetazidine (60 mg daily) for two years on top of conventional treatment significantly reduced the incidence of angina, recurrent angina, and silent ischemia compared with placebo. Moreover, these beneficial effects of trimetazidine were associated with a stabilization of cardiac function and structure.

Overall, these data suggest that the efficacy of trimetazidine in angina patients with diabetes goes beyond the relief of angina symptoms by providing additional benefits in terms of cardioprotection.

![In angina patients with left ventricular dysfunction](chart)

**In angina patients with left ventricular dysfunction**

A number of reports tend to indicate that trimetazidine could improve the cardiac function of patients with ischemic heart disease. In CAD patients with left ventricular dysfunction, 2 years’ treatment with trimetazidine (60 mg daily) on top of background therapy improved both myocardial perfusion and contractile function versus placebo, with single photon emission computerized tomography imaging. Trimetazidine was shown to increase left ventricular ejection fraction, reduce left ventricular volumes, and improve the quality of life of CAD patients with left ventricular dysfunction in various clinical settings, including in the elderly and diabetic patients.

Interestingly, the beneficial effects of trimetazidine on cardiac function observed in CAD may extend to heart failure, whether of ischemic origin or not. A recent meta-analysis of 17 randomized clinical trials in heart failure that included 955 patients treated with trimetazidine or placebo suggests so. Treatment with trimetazidine was associated with a significant improvement in left ventricular ejection fraction in patients with ischemic heart failure (weighted mean difference with placebo, +7.37%; 95% CI, 6.05 to 8.70; \(P<0.01\)) or nonischemic heart failure (weighted mean difference, +8.72%; 95% CI, 5.51 to 11.92; \(P<0.01\)). This was accompanied by a reduction in the...
risks of all-cause mortality (relative risk [RR], 0.29; 95% CI, 0.17 to 0.49; P<0.00001) and of cardiovascular events and hospitalization (RR, 0.42; 95% CI, 0.30 to 0.58; P=0.00001). These findings are further supported by a retrospective analysis of a cohort of 669 patients with heart failure, in which the use of trimetazidine was associated with improved survival from all-cause death and cardiovascular death.41

The addition of trimetazidine to conventional medical therapy is likely to improve cardiac function and prognosis in patients with left ventricular dysfunction and heart failure. Importantly, trimetazidine has a neutral effect at the hemodynamic level and can thus be safely used in these types of patient. Additionally, trimetazidine has been recognized as an effective anti-anginal treatment that is safe to use in heart failure and has been granted with class IIb of recommendation and level A of evidence in the latest ESC guidelines for heart failure treatment.23

◆ In angina patients with a history of myocardial infarction

Trimetazidine may also provide benefits in terms of outcomes in patients after myocardial infarction. The METRO study (ManAgeRnt of angina: a reTrospective cOhort) included 353 patients with stable angina treated with at least one antianginal drug (nitrates, β-blockers, calcium channels blockers, trimetazidine, or nicorandil) who had previously been hospitalized for myocardial infarction.42 Of all the antianginal strategies, only the one that included trimetazidine was associated with a significant reduction in all-cause mortality over 6 months following hospital discharge for myocardial infarction (odds ratio [OR], 0.36; 95% CI, 0.15 to 0.86; P=0.022).

Similarly, a retrospective analysis of a Korean registry that included 13,733 patients hospitalized for myocardial infarction showed that treatment with trimetazidine during the in-hospital period was independently associated with a significant reduction in all-cause mortality (hazard ratio [HR], 0.41; 95% CI, 0.18 to 0.97; P=0.042) and major adverse cardiac events (HR, 0.24; 95% CI, 0.10 to 0.56; P=0.001) over 12 months.43

These data suggest that trimetazidine, in addition to its clinical antianginal efficacy, may offer long-term cardioprotection by improving survival in patients after acute myocardial infarction.

◆ In angina patients with percutaneous coronary intervention

Although it is a minimally invasive procedure, PCI leads to myocardial injury in about one third of patients. A rise in troponin level immediately following PCI, a marker for myocardial injury, is correlated with a worse prognosis in these patients.44 The effect of trimetazidine has been investigated in a specific setting in a randomized study involving 266 angina patients undergoing elective PCI.46 Patients were randomized to trimetazidine (60 mg administered as a single dose 30 minutes before intervention) or no treatment. Treatment with trimetazidine prior to PCI limited periprocedural myocardial injury, as shown by the significant reduction in cardiac troponin Ic level up to 24 hours post-PCI in these patients compared with patients who received no treatment. Thus, the direct effect of trimetazidine on the cardiac cell may provide cardioprotection immediately after PCI.

A recent report investigated the effect of trimetazidine on the incidence of stent restenosis and major adverse cardiac and cerebrovascular events (MACCEs)—including all-cause mortality, nonfatal myocardial infarction, revascularization, stroke, and cerebral bleeding—in the control (gray bars; n=323) and trimetazidine (red bars; n=312) groups 12 months after percutaneous coronary intervention. Figure 4. Incidences of stent restenosis and major adverse cardiac and cerebrovascular events (MACCEs) including all-cause mortality, nonfatal myocardial infarction, revascularization, stroke, and cerebral bleeding in the control (gray bars; n=323) and trimetazidine (red bars; n=312) groups 12 months after percutaneous coronary intervention.

Overall, these findings suggest that beyond its antianginal effect, trimetazidine may improve prognosis in patients undergoing revascularization procedures. This hypothesis is currently being tested in the ATPCI (The efficAcy and safety of
Trimetazidine in Patients with angina pectoris having been treated by percutaneous Coronary Intervention study, a large morbidity-mortality trial in angina patients with a post-PCI follow-up of 2 to 4 years.

Conclusion

Trimetazidine is an antianginal treatment with well-established efficacy, whether as monotherapy or part of combination therapy (for patients inadequately controlled by hemodynamically active therapy alone). Based on its mechanism of action that directly targets the cardiac cell, trimetazidine provides robust antianginal efficacy, reduces the burden of myocardial ischemia, and improves exercise capacity in a variety of angina patients, including those with a history of myocardial infarction, previous PCI, diabetes, or left ventricular dysfunction. Moreover, data from clinical trials suggest that trimetazidine may also offer long-term cardioprotection in a broad range of cardiovascular patients.

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References

CIBLER LA CELLULE CARDIAQUE DANS L’ANGOR STABLE GRÂCE À LA TRIMÉTAZIDINE

L’angor est maintenant reconnu comme une maladie multiforme où l’obstruction coronaire ne constitue qu’un facteur de risque parmi d’autres. La cellule cardiaque, dont le rôle est central dans un grand nombre de processus ischémiques, est reconnue comme l’un des acteurs principaux de l’ischémie cardiaque. Au niveau cellulaire, l’ischémie myocardique se caractérise par un métabolisme énergétique myocardique modifié, résultant en un déséquilibre ionique, un mésusage et un déficit en énergie et aboutit finalement à un dysfonctionnement. Pendant l’ischémie, la trimétazidine agit directement au niveau cellulaire en diminuant l’oxydation des acides gras et en augmentant l’oxydation du glucose, ce qui contribue à rétablir un métabolisme énergétique normal. Ce mécanisme conduit à une amélioration globale du fonctionnement général de la cellule et exerce une action anti-ischémique au niveau des organes.

En ciblant directement la cellule cardiaque, le mécanisme d’action de la trimétazidine complète celui des traitements antiangoreux hémodynamiques, optimisant ainsi l’efficacité clinique lorsqu’elle est associée à d’autres traitements. La trimétazidine diminue les symptômes et augmente l’aptitude à l’effort des patients angoreux dont les symptômes sont mal contrôlés par les β-bloquants et/ou les antagonistes calciques. L’effet bénéfique de la trimétazidine a été démontré chez de nombreux patients angoreux, dont ceux ayant des antécédents d’infarctus du myocarde et ceux qui ont eu une intervention coronaire percutanée, un diabète ou une dysfonction ventriculaire gauche. En plus de ses effets antiangoreux prouvés, la trimétazidine peut aussi apporter d’autres effets bénéfiques en termes de cardioprotection et de pronostic chez de nombreux patients à risque cardiovasculaire.
Can you tell us what ATPCI stands for?

ATPCI (efficAcy and safety of Trimetazidine in Patients with angina pectoris having been treated by percutaneous Coronary Interventions [PCI]) is the short name of an international, multicenter, randomized, double-blind, placebo-controlled study in patients treated with trimetazidine for 2 to 4 years. The full title of the trial is “efficAcy and safety of Trimetazidine in Patients with angina pectoris having been treated by percutaneous Coronary Interventions.” The sponsor of the study is the Institut de Recherches Internationales Servier (I.R.I.S.) and it is registered with the World Health Organization (WHO) under the universal trial number (UTN) UIIII-1145-1743.

The acronym ATPCI is particularly appropriate for the study as it targets patients with ischemic heart disease who have received a percutaneous coronary intervention (PCI) and pharmacological treatment by trimetazidine—the active drug under testing, a piperazine derivative with anti-ischemic properties that are different from any other anti-ischemic drugs—a drug that increases the adenosine triphosphate (ATP) levels. The standard approach to treat coronary artery disease (CAD) is based on increasing oxygen supply to the myocardium and/or reducing oxygen consumption by means of hemodynamic effects, acting via the heart rate in the case of ivabradine, or via heart rate and myocardial contractility in the case of β-blockers and verapamil or diltiazem, and via the peripheral arterial coronary and/or venous resistance in the case of dihydropyridine calcium-channel blockers and nitrates. An alternative approach is to improve the efficiency and the energy of the heart for a given supply of oxygen, which is reduced during ischemia. In other words, such an approach aims to increase the level of ATP. This metabolic approach is interesting considering that trimetazidine does not have hemodynamic effects, but acts as a modulator of cardiac metabolism.

Under physiological conditions, the energy demand of the heart is met by the metabolism of two main substrates—glucose and free fatty acids (FFAs). Glucose metabolism occurs by means of glycolysis and oxidation. Whereas the oxidative pathway converts pyruvate into acetyl-coenzyme A (CoA), which is incorporated in the Krebs cycle and produces 36 molecules of ATP, the conversion of glucose to pyruvate during glycolysis produces only two molecules of ATP, but this ATP is important as oxygen is not required in the process. The FFAs are the main sources of ATP, corresponding to about 70% of the myocardial production, but the oxidation of FFAs requires about 10% more oxygen than that of glucose to produce an equivalent amount of energy. During ischemia and/or angina, all oxidative processes are depressed, leading to acetyl-coA accumulation in the mitochondria with a
block of FFA β-oxidation and of the activity of pyruvate dehydrogenase, the enzyme that allows the entry of pyruvate into the mitochondria. Pyruvate is then converted into lactic acid, which is released from the myocytes into the extracellular space, thus reducing the pH and causing pain by irritation of the myocardial nerve fibers. Thus, in ischemia, glycolysis, contrary to oxidation, continues in an anaerobic fashion, having as final product lactate instead of pyruvate, and becomes the only and most important source of anaerobic ATP.\(^1\) Trimetazidine further inhibits FFA β-oxidation and, indirectly, stimulates the activity of pyruvate dehydrogenase, thus directing pyruvate into the mitochondria, avoiding lactic acid formation, and allowing anaerobic glycolysis to continue. This has two important consequences—reduction in intra- and extracellular acidosis, thus preventing pain, and improvement in anaerobic ATP production through glycolysis, ensuring maintenance of cellular homeostasis and viability.\(^2\) As ancillary properties resulting from the maintenance of ATP, trimetazidine has also been shown to reduce oxygen free radical production and oxidative stress and to inhibit the opening of mitochondrial calcium pores with the consequent release of cytochrome C, thus reducing apoptosis and attenuating inflammation.\(^7\)

The acronym ATPCI is well-suited to this study, which aims to test whether treatment with trimetazidine to maintain ATP levels after PCI is useful to reduce symptoms and improve outcomes in patients with ischemic heart diseases.

**What is the rationale of the study and what is the main objective of ATPCI?**

ATPCI aims to assess the long-term efficacy and safety of trimetazidine versus placebo, when given in addition to other evidence-based cardiovascular therapies in patients having had a recent PCI. The rationale for ATPCI is based on three considerations.

The first is that, despite the wide use of PCI for patients with chronic or acute angina, it is not clear whether this intervention results in an improvement in outcomes when compared with medical therapy. In addition, several studies have shown that, after PCI, not all patients are angina free or stop the antianginal treatment.\(^3\)

The second consideration relies on the unique anti-ischemic and antianginal effects of trimetazidine, which could be ideal after PCI. The antianginal effect of trimetazidine in stable angina pectoris is well-known and documented by 25 studies, including more than 4000 patients, in which trimetazidine was compared with placebo or active comparator. Efficacy has always been assessed on ergometric criteria and symptoms.

In addition, a first Cochrane meta-analysis conducted in 2005, involving a total of 1378 patients, reported a statistically significant and clinically relevant efficacy of trimetazidine in the treatment of angina, either alone or in combination with conventional antianginal treatments.\(^4\) In 2012, a second Cochrane meta-analysis, including 2283 patients and two additional ergometric criteria—total exercise duration and time to onset of angina—confirmed the conclusion of the first meta-analysis (unpublished data). A third network meta-analysis was then conducted in 2011, including studies with positive results as well as studies with inconclusive results, as required by European guidelines. The conclusion was that trimetazidine is as efficacious as other antianginal agents despite the different mechanism of action.\(^5\)

The third consideration is related to the increasing evidence of microvascular dysfunction as a cause of angina. Trimetazidine, by improving energy metabolism, could be particularly useful in this setting, where classic agents, which mainly act on the epicardial coronary artery, are less likely to be active.

A previous proof-of-concept study showed a benefit of trimetazidine over placebo in reducing the incidence of recurrent angina in CAD patients after drug-eluting stent implantation.\(^6\) Another study showed a reduction in major adverse cardiovascular events after 1-year follow-up in patients who received trimetazidine for at least 1 month after PCI.\(^7\) A recent meta-analysis evaluates the effects of trimetazidine on patients undergoing PCI in a total of 778 patients.\(^8\) The additional use of trimetazidine, before intervention, reduced angina attacks and electrocardiographic changes during PCI and cardiac troponin level. It also improved the left ventricular ejection fraction.\(^8\)

**What is the study design and who are the target patients?**

ATPCI is a phase 3, international, multicenter, double-blind, placebo-controlled study randomized in two parallel and balanced arms—on top of post-PCI recommended treatment for CAD, patients receive either trimetazidine 35 mg twice daily or placebo—for both secondary prevention and regular antianginal therapies, as per current guidelines. Randomization at inclusion is stratified according to country and nature of PCI procedure, whether elective or urgent after an acute presentation but without STEMI.
A total of 5800 patients from 27 countries will be included within 30 days of PCI and followed-up during a 2- to 4-year treatment period with a maximum of 10 visits. ATPCI includes patients (women or men ≥21 years old and <85 years old of any ethnic origin) presenting with a single or multivessel CAD and having undergone PCI for at least one stenosis to either a native coronary artery or a coronary graft where the PCI fell into any of the following categories: (i) indicated because of angina pectoris occurring either in the context of stable angina (elective PCI) or in the context of an acute presentation, such as unstable angina/non-ST-segment elevation myocardial infarction (NSTEMI), but excluding ST-segment elevation myocardial infarction (STEMI); (ii) achieved by stent implantation or by other acceptable interventional (nonsurgical) means; (iii) successful as planned by the operator and with no further revascularization (either percutaneous or surgical) planned; or (iv) uncomplicated, such that the patient’s discharge was not delayed because of a cardiac or cerebrovascular problem.

A measurement of left ventricular ejection fraction (LVEF) needs to be performed within 3 months before inclusion for patients having undergone elective PCI and between PCI and inclusion for patients having undergone index PCI performed in the context of an acute syndrome. Patients can be selected after PCI regardless of whether they are asymptomatic or symptomatic with regard to angina, and regardless of their Canadian Cardiovascular Society (CCS) class.

What is the primary end point of the study?

The primary efficacy end point of ATPCI is the time to first occurrence of an event in the composite of: (i) cardiac death; (ii) hospitalization for a cardiac event; (iii) recurrent or persistent angina leading to adding, switching, or increasing the dose of one of the evidence-based antianginal therapies; and (iv) recurrent or persistent angina, leading to performance of a coronary angiography, all of which will be reviewed by an independent adjudication committee. The primary safety end point is the incidence of serious emergency adverse events (in all visits) with trimetazidine as compared with placebo.

The secondary end points are the time to first occurrence of each of the separate four components of the primary end point, with the addition of evidence of ischemia (documented by stress imaging and leading to adding, switching, or increasing the dose of one of the evidence-based antianginal therapies). Other efficacy end points include the following: CCS class of angina symptoms, number of angina episodes per week, number of doses of short-acting nitrates taken per week, number of antianginal drugs taken by the patient, Seattle Angina Questionnaire scores (in countries where a validated translation is available), EQ-5D-3L Questionnaire scores, and level of cardiac troponin (before each repeat PCI and between 6 and 24 hours after).

What might we expect from the study?

ATPCI will improve our knowledge of CAD and its treatment by PCI. It will also identify the role of metabolic therapy in this setting of patients. It is the first study to test the value of increasing the energy status of the ischemic myocyte with trimetazidine in terms of hard end points such as cardiac death and hospitalization. This is particularly relevant considering that a recent study with ranolazine, another piperazine derivative, in a similar patient setting failed to show a benefit.9

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Keywords: angina; cardiac metabolism; percutaneous coronary intervention; trimetazidine

References
Myocardial ischemia can be looked at as a metabolic problem, as it leads to an imbalance in the pathways the normal heart relies on for energy production. Use of pharmacological agents to optimize cardiac energy metabolism by stimulating myocardial glucose oxidation can be an effective therapeutic option. The metabolic agent trimetazidine does this indirectly by inhibiting fatty acid β-oxidation, in effect changing the energy substrate preference, promoting a shift from fatty acid metabolism toward glucose metabolism, which is more efficient for ATP production. The efficacy of trimetazidine in the treatment of angina pectoris has been evaluated under various conditions: trimetazidine administered as a monotherapy or in combination, acutely or over a longer-term period, as initial treatment, and in patients resistant to β-blockers or calcium-channel antagonists. All published studies employing trimetazidine in patients with chronic ischemic heart disease have invariably reported beneficial clinical effects without adverse hemodynamic events. In fact, in chronic ischemic heart disease patients with left ventricular dysfunction, trimetazidine has been shown to be a particularly effective adjunctive treatment in terms of improvement in left ventricular metabolism and function. An ongoing randomized clinical study in patients with revascularized coronary artery disease should clarify whether the reported experimental and clinical benefits of trimetazidine also translate into improved prognosis.

Ischemic heart disease is a major cause of morbidity and mortality worldwide. In patients with acute coronary syndromes, revascularization interventions have been shown to reduce myocardial infarction and death; however, this is not the case in patients with chronic stable angina. In fact, according to the European Society of Cardiology (ESC) and the European Association for Cardio Thoracic Surgery (EACTS) 2014 guidelines, percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) should be reserved for patients with refractory angina and for patients in whom such procedures would be expected to provide a survival benefit; this would be influenced by a number of factors, such as the number of diseased vessels, lesion location and severity, and the presence of left ventricular dysfunction. Thus, all patients with stable ischemic heart disease, whether they are asymptomatic or experiencing severe symptoms, should first receive optimal medical therapy, which would usually be maintained even after revascularization.
Current anti-ischemic/antianginal therapy focuses on two major actions. The first pertains to vascular protection, in this case aiming to delay progression of atherosclerosis (by use of statins, antithrombotic drugs), which would reduce future cardiovascular events and death and improve quality of life. The second pertains to improvement in the imbalance between myocardial oxygen supply and demand (ischemic imbalance), which would reduce the severity and frequency of angina symptoms and also contribute to improvement in quality of life. However, this therapeutic view does not consider the cardiac metabolic consequences of myocardial ischemia. In fact, ischemia can be thought of as a metabolic problem (previously discussed in Salerno et al4), because it leads to an imbalance in the pathways the normal heart relies on for energy production. Under normoxic conditions, the healthy heart generates approximately two-thirds of its energy (in the form of adenosine triphosphate, ATP) from the free fatty acid (FFA) pathway; the remaining energy production is derived from glucose oxidation and lactate.5-7 Under hypoxic conditions, such as mild-to-moderate ischemia, myocardial cells turn to another more oxygen-efficient pathway to generate sufficient ATP to support calcium homeostasis and maintenance of ionic gradients: their response is to increase glucose uptake, as glycolysis requires less oxygen per mole of ATP generated than FFA oxidation. Severe ischemia, however, rapidly induces an imbalance between cardiac tissue oxygen demand and the available coronary blood supply. Changes in myocardial function, metabolism, and morphology ensue, leading to arrhythmias, contractile failure, and electrophysiological abnormalities. Myocardial cell uptake of glucose decreases and conversion to lactate increases; there is a switch from lactate uptake to lactate production, and most pyruvate is transformed into lactate, increasing cell acidosis. Concurrently, use of the FFA pathway slows, and overall ATP production decreases. The results of such metabolic changes include the disruption of cell homeostasis, alterations in membrane structure, and ultimately cell death.

This review discusses the rationale behind a pharmacological approach to stop this vicious circle in patients with chronic ischemic heart disease.

**Medical treatment of chronic ischemic heart disease**

In addition to lifestyle and hygienic dietary measures, guideline-recommended first-line treatment for patients with stable angina includes aspirin, statins, and β-blockers. This recommendation is consistent across all guidelines for the diagnosis and management of this condition. The main probable mechanism by which β-blockers relieve anginal symptoms is a reduction in both heart rate and contractility. However, their indication as a first-line treatment is still under debate. They are given a class I indication for the treatment of chronic angina, mainly on the basis of a general agreement on the issue, whereas they are attributed a level of evidence A on the basis of studies that were carried out in patients after a myocardial infarction or heart failure, in which they consistently decreased morbidity and mortality. However, several reports have discussed potential pitfalls in their use in patients with stable coronary artery disease (CAD). In the REACH registry (REduction of Atherothrombosis for Continued Health), β-blockers were not associated with a lower risk of composite cardiovascular events, and they were associated with higher rates for the secondary outcome (comprising primary outcome and hospitalization for atherothrombotic events or a revascularization procedure) in chronic CAD patients.8 A recent post-hoc analysis of the CHARISMA study (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization Management and Avoidance) indicated that use of β-blockers in patients that had a previous myocardial infarction but no heart failure was associated with a better cardiovascular prognosis—determined by reduced reinfarction rate—but did not reduce overall mortality. Additionally, in patients without previous myocardial infarction, β-blockers did not reduce cardiovascular events but were rather associated with a higher incidence of stroke, confirming previous meta-analyses of studies performed in hypertensive patients.9 The hypothesized mechanism to explain these potential deleterious effects of β-blockers is related to an insufficient reduction in central aortic pressure, potentially related to heart rate reduction, which in certain contexts would not play a positive role. Therefore, there is still no clear evidence from randomized clinical trials for the efficacy of β-blockers used in first-line treatment in patients with chronic stable angina. Yet, we enthusiastically continue to use them.

If a patient continues to complain of symptoms after the first-line treatment scheme has been implemented, other drugs, such as calcium-channel blockers or long-acting nitrates, could be prescribed. Calcium-channel blockers (mostly dihydropyridine derivatives) cause coronary and peripheral vasodilation (but increase heart rate and partially reduce the beneficial heart rate–lowering effect of β-blockers); the phenylalkylamine derivative verapamil and, to a lesser extent, diltiazem (benzothiazepine calcium-channel blocker) reduce heart rate and
contractility and are used when β-blockers are contraindicated. Combining verapamil or diltiazem with β-blockers yields additive effects in terms of bradycardia, heart block, and negative inotropic effects. When added to β-blockers or calcium-channel blockers, long-acting nitrates improve exercise tolerance, increase time to onset of angina, and reduce ST-segment depression during exercise testing; however, their use is limited by the development of tolerance on long-term administration. In summary and similarly to β-blockers, there is no clear-cut evidence of the prognostic utility of these additional antianginal drugs in chronic CAD. Furthermore, conflicting evidence exists about combining antianginal hemodynamic drugs.

Having said this, pharmacological treatment of chronic ischemic heart disease continues to be based mostly on β-blockers, calcium-channel blockers, and nitrates. In most cases, if symptoms are not brought under control by treatment with a single traditional antianginal drug, a drug combination would be used, with the addition of a second or third agent. However, there are no clinical studies demonstrating a real additive efficacy of a combination of classic hemodynamically active drugs as compared with monotherapy. Furthermore, significant side effects may limit the maximal doses that can be used for such drugs, especially in an aged population. In such a context, the use of alternative therapeutic approaches would be warmly welcomed and, with this in mind, pharmacologically addressing the underlying derangements in cardiac metabolism, discussed next in further detail, could be a rational solution to this problem.

Pharmacological manipulation of cardiac energy metabolism

Given the above-described pathophysiology of ischemic heart disease and the difficulties encountered with many patients when trying to control the total ischemic burden with classic hemodynamically active drugs, an adjunctive therapeutic option that pharmacologically manipulates cardiac energy metabolism seems reasonable (previously discussed in Salerno et al). This approach is based on stimulating myocardial glucose oxidation to optimize cardiac energy metabolism, and is proven to improve cardiac function and protect myocardial tissue against ischemia-reperfusion injury. Myocardial glucose oxidation can be promoted either directly by stimulating glucose metabolism or indirectly by inhibiting fatty acid β-oxidation, producing a shift of energy substrate utilization away from fatty acid metabolism and toward glucose metabolism, a more oxygen-efficient path to ATP production (more ATP produced per mole of oxygen used). Indeed, oxygen consumption efficiency in the heart can be improved within the range of 16% to 26% by the increased use of glucose and lactate—more efficient fuels for aerobic respiration.

Additionally, the uptake of glucose in the heart and arm skeletal muscle has been shown to be inversely related to serum FFA levels, and an increased flux of FFA from adipose tissue to nonadipose tissue exacerbates metabolic abnormalities characteristic of the insulin resistance syndrome, a common pattern in patients with ischemic heart disease. Furthermore, there is new evidence that elevated levels of FFA may not only impair glucose uptake in heart and skeletal muscle but also alter metabolism in the vascular endothelium, which leads to premature cardiovascular disease. These findings suggest that metabolic therapy could have a beneficial role in glucose metabolism homeostasis.

Manipulation of cardiac energy metabolism through a number of approaches has been investigated. Trimetazidine is the most extensively studied cardiac metabolic drug and has been shown to increase glucose oxidation and reduce FFA utilization, restoring cardiac coupling between glycolysis and glucose oxidation. The next section will look more closely at the beneficial effects of cardiac metabolic manipulation by trimetazidine in ischemic heart disease.

Complementary role of trimetazidine in ischemic heart disease

Trimetazidine’s use in patients with ischemic heart disease has consistently provided clinical benefits (previously discussed in Salerno et al). Although its mechanism of action is still under debate, experimental evidence indicates that trimetazidine exerts its effects predominantly through partial inhibition of mitochondrial long-chain 3-ketoacyl coenzyme A thiolase, the last enzyme involved in β-oxidation, in effect causing a switch in energy substrate use away from FFA to glucose and lactate. As mentioned briefly in the previous section, the resulting reduction in FFA oxidation and increase in glucose oxidation restores the myocardial coupling between glycolysis and carbohydrate oxidation, allowing ATP production with less consumption of oxygen. Trimetazidine also promotes membrane phospholipid turnover during ischemia and reperfusion, redirecting FFA toward phospholipids and thus increases the cell’s tolerance to ischemia-reperfusion damage. Trimetazidine’s anti-ischemic actions are independent of hemodynamic changes and are associated with a greater recovery of mechanical function after ischemia.

Trimetazidine’s efficacy in the treatment of angina pectoris has been investigated under various conditions: trimetazidine administered as a monotherapy or in combination, acutely or over a longer-term period, as initial treatment, and in patients resistant to β-blockers or calcium-channel antagonists. Initially studied in patients with chronic stable effort angina during exercise testing, acute administration of trimetazidine increased effort tolerance and delayed the appearance of ischemic symptoms and electrocardiogram changes.

With long-term treatment, the benefits seen with acute administration were confirmed. Such treatment was well-tolerated, with no appreciable side effects, including no significant
Combining hemodynamic and metabolic agents in ischemic heart disease – Fragasso

Changes in heart rate and/or aortic pressure. In comparison studies, improvement in ischemic threshold and exercise tolerance on trimetazidine treatment is similar to that reported for propranolol and nifedipine, and there was even a lower incidence of side effects. Trimetazidine’s effects were shown to be additive to those of hemodynamically active drugs, with direct evidence provided by a randomized, double-blind study in patients with chronic effort angina and documented CAD. This study compared the combination of trimetazidine plus the β-blocker propranolol with nitrates plus propranolol, and found that the combination including trimetazidine was not only more effective and better tolerated than the other combination, but also the only one that showed improvement. The other combination had no effect on symptoms and exercise capacity. In another randomized, double-blind study in patients with angina uncontrolled by diltiazem, the addition of trimetazidine to a full-dose diltiazem treatment scheme yielded beneficial effects. In yet another study, this time in patients with stable effort angina uncontrolled by metoprolol alone, 12-week treatment with trimetazidine and metoprolol significantly reduced clinical symptoms compared with placebo and metoprolol. A previous study, TRIMPOL-I (TRIMetazidine in POLand), had already shown that in diabetic patients, 4 weeks of treatment with trimetazidine was associated with a significantly lower number of anginal episodes and an improvement in myocardial ischemia and exercise capacity.

In diabetic patients with chronic stable angina, Marazzi et al have shown that trimetazidine added to standard medical therapy reduces the number of episodes of ST-segment depression and silent ischemia and reduces total ischemic burden. In patients with stable angina pectoris, the efficacy of trimetazidine was significantly induced an increase in the administered dobutamine dose (panel A) versus placebo. Despite a higher administered stress, left ventricular function (assessed by wall motion score index) was significantly less impaired when patients were on trimetazidine (panel B). These findings indicate that metabolic therapy added to treatment schemes yields a better response to stress.

**Figure 1.** Bar charts showing mean (+1 standard deviation) glucose infusion rate at the hyperinsulinemic/euglycemic clamp during short-term (15 days) and long-term (6 months) placebo and trimetazidine administration in patients with chronic ischemic heart disease, left ventricular dysfunction, and diabetes. The infusion rate of glucose necessary to maintain euglycemia after an insulin bolus was greater when patients were on trimetazidine, both in the short and long term. This indicates that in these high-risk patients, trimetazidine, compared with placebo, was also able to significantly improve insulin sensitivity.

**Figure 2.** Insulin sensitivity. Bar chart showing mean (+1 standard deviation) glucose infusion rate at the hyperinsulinemic/euglycemic clamp during short-term (15 days) and long-term (6 months) placebo and trimetazidine administration in patients with chronic ischemic heart disease, left ventricular dysfunction, and diabetes. The infusion rate of glucose necessary to maintain euglycemia after an insulin bolus was greater when patients were on trimetazidine, both in the short and long term. This indicates that in these high-risk patients, trimetazidine, compared with placebo, was also able to significantly improve insulin sensitivity.
Trimetazidine was found to be comparable to that of other drugs that have no influence on heart rate (ie, other non-heart-rate-lowering antianginal drugs).29

Trimetazidine has also been confirmed to be effective in different settings of stable coronary disease,30-32 expanding its use to include patients with heart failure both of ischemic and nonischemic origin.33,34 In such contexts, trimetazidine improves symptoms, cardiac response to ischemia, left ventricular function (Figure 1, page 323),32 and thus quality of life as well. The main mechanism of action is probably through a trimetazidine-induced increase in myocardial cellular energy reserve.35 However, improved endothelial function36 and increased insulin sensitivity33,36 (Figure 2, page 323) may also play a role; it is possible that indirect beneficial electrophysiological effects37 (Figure 3) may also be involved. Long-term administration of trimetazidine has also been shown to improve survival and event-free survival in patients with ischemic and nonischemic left ventricular dysfunction (Figure 4).38

Similarly to other established antianginal drugs, the main limitations on the wide use of trimetazidine in chronic ischemic heart disease include the paucity of data on mortality and major cardiovascular events and on direct comparisons between trimetazidine and established antianginal therapies. Nevertheless, in 2005, a Cochrane review including 23 studies (1378 patients) concluded that trimetazidine is a well-tolerated drug that provides benefit in patients with stable angina, in terms of patient-reported intake of glyceryl trinitrate tablets and number of weekly angina episodes when used as monotherapy and in combination with conventional antianginal agents.39 A more recent meta-analysis (13 studies, 1628 patients) that compared trimetazidine with conventional antianginal drugs confirmed the efficacy of trimetazidine treatment for stable angina pectoris, regardless of treatment duration.40

At present, the European Society of Cardiology indicates trimetazidine as an effective adjunctive treatment in patients with angina not completely controlled by standard hemodynamic therapy.41

**Figure 4.** Effects of trimetazidine versus conventional therapy alone (control) on 5-year global and cardiovascular mortality in patients with ischemic and nonischemic left ventricular dysfunction.

The histogram on the left shows an 11.3% reduction in 5-year global mortality when trimetazidine (TMZ) is administered in addition to standard medical therapy (P=0.015). The histogram on the right shows an 8.7% reduction in 5-year cardiovascular mortality in the same patients (P=0.05).

**Abbreviations:** CV, cardiovascular; TMZ, trimetazidine.


**Figure 3.** Baseline and follow-up Tpeak-Tend dispersion (mean + 1 standard deviation) in patients with left ischemic and nonischemic left ventricular dysfunction and treated with trimetazidine (red columns) or conventional therapy alone (controls; grey columns).

Tpeak-Tend dispersion index is a noninvasive marker of dispersion of ventricular repolarization and is positively related to the risk of arrhythmias. The evidence of a significant TMZ-induced Tpeak-Tend dispersion reduction only in patients with post-ischemic left ventricular dysfunction supports the hypothesis that the potential antiarrhythmic properties of TMZ could be directly mediated by the anti-ischemic action of the drug.

**Abbreviations:** TMZ, trimetazidine.


**Combined metabolic action of β-blockers and trimetazidine**

Despite their above-described pitfalls, β-blockers continue to be the clinical mainstay of ischemic heart disease treatment. They act principally through reduction in oxygen consumption by reducing heart rate and inotropism. However, they could have a direct complementary metabolic effect themselves, by reducing peripheral lipolysis and reducing FFA availability. Indeed, there is evidence that β-blockade reduces FFA use in favor of greater glucose use in cardiac patients.42 Such a change in cardiac energy metabolism could be a potential mechanism...
for the decreased cardiac oxygen consumption and improvement in energy efficiency observed with β-blocker treatment of ischemic heart disease and heart failure.43 Whether nonselective β-blockers are more efficient than selective ones in shifting whole-body substrate utilization from FFA to glucose oxidation44 is still under debate.45 Nonetheless, the better survival rates observed with nonselective β-blockers could be explained by their effect on the metabolism.46 Additionally, inhibition of activity in the sympathetic nervous system with the centrally acting antihypertensive drug moxonidine has been associated with increased mortality in patients with chronic heart failure.47 In fact, despite a significant reduction in catecholamine spillover from the synapses in the sympathetic nervous system—thus reducing catecholamine levels in the blood—and, consequently, heart rate, moxonidine increases both FFA use and myocardial oxygen consumption.48 This could be the reason why central sympathetic inhibition fails to prevent deaths in long-term studies in patients with chronic heart failure; it also indicates that the main mechanism of action of β-blockers in cardiac syndromes probably involves something other than a simple reduction in heart rate. Thus, it is possible that the degree of heart rate reduction is just a marker of the functional response after the administration of β-blockers, ie, a consequent effect rather than a mechanism. On this basis, we can hypothesize that β-blockers and trimetazidine have a complementary, synergistic metabolic action: whereas the former reduces FFA availability, the latter decreases their cardiac utilization. Overall, this drug-induced metabolic shift could reduce FFA oxidation and increase flux through pyruvate dehydrogenase with a consequent energy-sparing effect.35,49

There is evidence to suggest that trimetazidine’s metabolic effect may occur in other organs and tissues as well.50 In fact, apart from a reduction in whole-body energy demand, a trend for a reduction in whole-body lipid oxidation and in fasting plasma FFA concentration has also been observed (Figure 5).50 This general metabolic shift could in the end reduce the overall metabolic requirements of the body, resulting in a very attractive adaptation strategy in the context of coronary and myocardial insufficiencies. Interestingly, β-blockers have also been shown to directly affect whole-body metabolism. In trained athletes, β-blockade abolishes the increase in plasma glucose levels that occur during intense exercise, owing to an increased peripheral glucose uptake and no significant change in glucose production.51 Such effects from β-blockade on glucose kinetics could be mediated directly; they could also be indirectly mediated through changes in lipid substrates and/or counter-regulatory hormones.

Potential role of metabolic therapy in revascularized chronic ischemic heart disease

Despite no clearly demonstrated prognostic gain, nowadays, revascularization procedures are often considered first for the control of angina pectoris. However, recurrent or persistent angina after initially successful revascularization is not infrequent and is frustrating for patients and doctors. In fact, subsequent repeat coronary angiography and revascularization procedures introduce both additional risk for the patient and cost to the health care system. A more effective medical strategy could certainly improve the management of these patients. In this context, an ongoing international, multicenter, randomized clinical study would provide the cardiological community with new solid data in a few years’ time. The purpose of the ongoing ATPCI study (efficAcy and safety of Trimetazidine in Patients with angina pectoris) having been treated by percutaneous Coronary Intervention; EudraCT Number: 2010-022134-89) is to evaluate the long-term efficacy and safety of trimetazidine, in addition to evidence-based cardiovascular therapy, in patients having had a recent percutaneous coronary intervention. The primary objectives are to demonstrate the superiority of trimetazidine over placebo in preventing recurrence or exacerbation of angina pectoris and in reducing cardiac events, and also to document its safety by analyzing the occurrence of serious adverse events. Apart from the evaluation of the effects of trimetazidine in this widely encoun-

Figure 5. Bar chart showing mean (+ 1 SD) resting energy expenditure (kcal/day) at baseline and after 3 months of follow-up in patients with ischemic and nonischemic left ventricular dysfunction treated with conventional therapy plus trimetazidine (red columns) or conventional therapy alone (grey columns).

Trimetazidine significantly reduces the whole-body energy expenditure, indicating a potential role of this metabolic drug on overall metabolic requirements of the body. Based on data from reference 50: Fragasso et al. Heart. 2011;97:1495-1500.

Conclusions

Optimization of cardiac energy metabolism is attractive as an approach to protect myocardial cells from ischemia and to improve performance of dysfunctional myocardium. To that effect, trimetazidine, which shifts the energy substrate preference away from FFA metabolism toward increased glu-
cose oxidation, has been shown by a number of studies to be an effective adjunctive treatment in patients with chronic ischemic heart disease and heart failure, reducing ischemic burden and improving left ventricular metabolism and function. Whether the reported experimental and clinical benefits translate into improved prognosis is currently being ascertained by an ongoing international randomized clinical trial. This has potential to be a major therapeutic advance in chronic ischemic heart disease patients, who continue to experi-

ence very high morbidity and mortality rates in spite of treatment efforts. Furthermore, most cardiac diseases are associated with derangements in glucose homeostasis, which certainly contribute to primary disease progression. An advantage of trimetazidine treatment is the combined beneficial effects that FFA inhibitors have on left ventricular function and glucose metabolism, which would be especially advantageous in cardiac patients with coexisting myocardial dysfunction and glucose metabolism abnormalities.

References
L’association d’agents hémodynamiques et métaboliques dans la cardiopathie ischémique

L’ischémie myocardique peut être considérée comme un problème métabolique conduisant à un déséquilibre des voies utilisées normalement par le cœur pour produire de l’énergie. L’utilisation d’agents pharmacologiques pour optimiser le métabolisme énergétique cardiaque en stimulant l’oxydation du glucose au niveau du myocarde peut être une option thérapeutique efficace. Ainsi, la trimétazidine est un agent métabolique qui agit indirectement en inhibant l’oxydation des acides gras, ce qui privilégie le métabolisme du glucose, un substrat énergétique plus efficace pour la production d’ATP que les acides gras. L’efficacité de la trimétazidine dans le traitement de l’angor a été évaluée dans différentes conditions : administration de la trimétazidine en monothérapie ou en association, en période aigüe ou à plus long terme, en traitement initial, et chez les patients résistants aux β-bloquants ou aux inhibiteurs calciques. Toutes les études publiées employant la trimétazidine chez des patients ayant une cardiopathie ischémique chronique ont invariabi…
Coronary stenting represents a major step in the history of percutaneous coronary angioplasty. Jacques Puel performed the first stent implantation in man in 1986, and research in the area took off immediately. The primary concern about balloon angioplasty procedures was safety, as there is a risk of abrupt occlusion during the procedure. This risk and the subsequent need for emergency bypass surgery were dramatically reduced with stent implantation. Nevertheless, investigators then faced another problem: the risk of stent thrombosis. However, such risk is suppressed by the use of a dual antiplatelet treatment. Coronary stenting has now played a major role in the fight against restenosis, with drug-eluting stents considerably reducing this risk, even in high-risk patients (diabetics). With coronary stenting, coronary interventional procedures have become the primary approach to myocardial revascularization.

Medicographia. 2016;38:328-334 (see French abstract on page 334)

The first coronary angioplasty in man was performed by Andreas Gruentzig from Zurich (Switzerland) in September 1977. This new, noninvasive approach for myocardial revascularization would have an immediate and great success. In the years that followed, significant technical improvements were proposed. The over-the-wire technique, designed by John Simpson, and the monorail system were rapidly adopted by the interventional cardiology community. However, new problems were observed: the most important pertained to the safety of the procedure. During or immediately after angioplasty, an abrupt occlusion of the vessel was observed in 3% to 5% of cases. This accident was related to an occlusive dissection or an occlusive thrombosis of the vessel. Thus, when use of coronary angioplasty was beginning, it was recommended to perform the procedure with a surgical backup, enabling immediate emergency bypass surgery if needed. In most cases, this emergency operation was followed by limited myocardial necrosis. Aside from this immediate problem, 30% to 45% of cases experienced later restenosis in a process such as the following: the mechanism of initial enlargement of the lumen was through dissection of the vessel; and this dissection was followed by a process of healing, which involved migration and proliferation of smooth muscle cells into a loose extracellular matrix; thus, intimal hyperplasia occurred, contributing to the renarrowing of the dilated vessel. Later, it was discovered that another important phenomenon was occurring—negative remodeling of the vessel, leading to shrinkage of the dilated segment. It is within this context that coronary stenting arose and solved, at least partially, the two major problems of coronary angioplasty, namely abrupt occlusion and restenosis.
### History of stenting

It has been said that the Egyptians tried to cure the narrowing of urethra by introducing a small reed in the urinary canal in order to reestablish a more fluid relationship between the internal and external milieu.

In September 1912, the French surgeon, Alexis Carrel made a prophetic statement following the publication of his work on permanent intubation of the thoracic aorta in dogs:

> The permanent intubation of a large vessel is a simple operation. It may become practical, if the shape and the nature of the tube be modified as to avoid lacerations (...). The question of the application of this method to human surgery may then, possibly, be considered.

It took more than 70 years to verify this assumption.

The first stent was conceived from the progress in therapeutic intervention initiated by Charles Dotter; he was a true inventor and a pioneer in the interventional cardiovascular world. He opened the way for interventional cardiology, and he started to design the first vascular stent at the end of the 1980s with insertion of plastic tubes and collapsible stainless-steel prostheses into the femoral or popliteal arteries of dogs.

In 1978, a young fellow who had recently arrived from Argentina attended a lecture by Andreas Gruentzig at a meeting of the Society of Cardiovascular and Interventional Radiology. His name was Julio Palmaz, and he thought that “the problems that doctor Gruentzig had with his balloon could be avoided by inserting some sort of a scaffold at the time of dilatation.” The chairman of the department said that it could be a nice research project. After writing a report and making drawings, he started to build a prototype in his garage with copper wire and solder materials.

The wire was woven in a crisscross mesh around a pencil with two rows of pins. Solder was used to fix the cross points to allow the mesh to retain its shape. Once built, the mesh diameter was decreased by compressing it on progressively smaller wooden dowels and then was crimped by hand on a folded balloon. However, the material was excessively rigid, and the slots and the spaces between were inadequate. Julio Palmaz searched for a manufacturer, but several companies refused to consider this device.

In Switzerland, the story of stenting started during a party: two Swedish persons met—one, Hans Wallstén, was the designer of a revolutionary machine intended to manufacture paper; the other, Ake Senning, was a well-known cardiovascular surgeon. During the meeting, Senning explained that aortic dissection was a very serious acute disease and went on to detail his concept of a mechanical scaffolding of the arterial wall by a latticed metallic tube. Wallstén, very excited, decided to take up the problem of metallic endoprostheses. He created the Wallstent but had some difficulties finding a solution for a percutaneous approach; the solution was found by the engineer Christian Imbert. The self-expandable stent, which could be implanted via a percutaneous femoral approach, was thus created. Looking for centers to experiment with his device, Christian Imbert met Ulrich Sigwart in Lausanne and the group of Jacques Puel in Toulouse.

In cooperation with radiologists from Toulouse, Jacques Puel conducted experiments in sheep and dogs. These experiments quickly (probably too quickly) met with success and showed, at least at first glance, that it was easy (possibly too easy) to implant the endocoronary prosthesis percutaneously and that rapid endothelialization of the struts occurred. However, these animal experiments did not reveal the high risk of subsequent thrombosis. Later, Puel confessed that he had probably underestimated this risk. Simultaneously in Lausanne, Ulrich Sigwart was conducting experimental implantation in dogs.

The first stent implantation in man was performed on March 28, 1986 by Puel using the Wallstent. The medical history of this first patient is quite simple: the patient was a 63-year-old male with arterial hypertension and symptomatic restenosis 6 months after treatment of a mid–left anterior descending artery lesion (Figure 1). In 1986, with evidence-based medicine...

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**Figure 1. First stent implantation in man.**

Stent implantation in a 63-year-old male with arterial hypertension and symptomatic hypertension 6 months after treatment of a mid–left anterior descending artery lesion. The procedure was carried out by Jacques Puel in 1986. 

A. Angiogram showing high-grade stenosis of the proximal left anterior descending artery (yellow arrow) before the procedure. B. The bare metal stent used in the procedure. C. Angiogram showing the stent in place (yellow arrow). All rights reserved.
still in its infancy, the patient received no antiplatelet drugs or statins in preparation for stent implantation; rather, he received only subcutaneous heparin during the procedure and within the next 6 weeks. By chance, he had no stent thrombosis or in-stent restenosis within that time span; however, he did not escape progression of the atherosclerotic process and had had recurrent episodes of angina pectoris related to a new lesion on the ostium of the left anterior descending artery and another one on the circumflex artery, which was treated in 2004 by a new stent implantation. In the weeks after that first implant, seven other patients received a self-expandable Wallstent without any complications.

In Lausanne, the results obtained from 9 months of animal experiments were convincing enough to persuade the Institutional Review Board to give approval in April 1986 for the use of stent implants for three indications: abrupt vessel closure after balloon angioplasty, restenosis after balloon angioplasty, and stenosis of saphenous vein bypass grafts. After a number of deployments in human femoral and iliac arteries, the self-expanding mesh stent was first deployed after balloon dilatation of a tight stenosis in a vein bypass procedure.

Although initial results were promising, they were misleading—the next four patients to undergo the stent procedure experienced a subacute stent thrombosis. With a single antithrombotic treatment using full-dose heparin, the risk of thrombosis was very high.

Later, Ulrich Sigwart would perform the stent implantation procedure under full anticoagulation treatment with heparin followed by oral anticoagulation with warfarin. This medical treatment slightly decreased the risk of stent thrombosis, though it remained very high (occurring in 5% to 10% of cases).

These two clinical trials, conducted initially in Toulouse and later in Lausanne, proved the feasibility of the stent implantation method. However, they also demonstrated the high potential thrombogenic risk posed by introduction of this foreign body; nevertheless, stents markedly reduced the risk of acute or subacute occlusion. As a result, the need for emergency surgical bailout procedures was drastically reduced (Figure 2).

The evolution of coronary stenting over the years that followed can be divided into three different parts—technical improvement, safety improvement, and restenosis prevention and treatment. These will be discussed in turn.

**Technical improvements in stenting**

A number of variations of the stent have been proposed over the years. The first stent implanted in the coronary arteries in man was the Wallstent (Medinvent). It was a self-expanding stent composed of 20 strands of 0.06 to 0.09 mm diameter arranged into a self-expanding mesh design. It was flexible; its length ranging from 15 to 30 mm; and its diameter between 3.0 to 6.0 mm. The mesh was compressed and elongated on the delivery catheter owing to a double wall sleeve membrane. Retraction of this membrane allowed the progressive release into the vessel.

The aforementioned work of Julio Palmaz led to creation of a tubular slotted stent; together with Richard Schatz, it was implanted in coronary arteries for the first time in December 1987 (Figure 3B). This was a balloon-expandable stent crimped on the delivery catheter, and it became very popular. The Gianturco Roubin stent (approved in the United States in 1993) (Figure 3C) had a poor radial strength, which was responsible for an increased rate of restenosis and stent thrombosis. Later, Medtronic proposed a coil stent or Wiktor stent (Figure 3D). Finally, stents covered by a membrane of polytetrafluoroethylene were proposed
and used in saphenous vein graft stenoses to avoid the embolization of the friable materials characteristic of these lesions. It was also used for the emergency treatment of coronary perforations.

Drug-eluting stents were introduced in 2000. They are composed of two parts: the polymer coating the strut (one or several layers) and the drug delivered into the vessel wall. The drugs act on the cell cycle (Figure 4) and are able to suppress smooth muscle cell proliferation without toxicity and with a low inflammatory risk. Most drug-eluting stents use an analog of sirolimus (drugs used from the limus group include sirolimus, everolimus, zotarolimus, biolimus, the sirolimus metabolite novolimus, and myolimus, a macrocyclic lactone close to the rapamycin family).

The first drug-eluting stent of this group was the Cypher (Cordis Corporation). Almost simultaneously proposed was paclitaxel, which inhibits cell replication and is the drug delivered by the Taxus stents (Boston Scientific). Cypher and Taxus stents were the first-generation drug-eluting stents. These were followed by second-generation (followed by a second generation (Xience, Endeavor stents) and third-generation drug-eluting stents, the latter being fully bioresorbable vascular scaffolds (BVS), including: (Igaki-Tamai (Igaki Medical Planning), BVS 1.0 (Abbott Vascular), DESolve (Elixir Medical Corporation), REVA (Reva Medical), ART 18AZ (Arterial Remodeling Technologies), and Amaranth stents.

Safety improvements in stenting: the fight against acute or subacute stent thrombosis (first revolution in coronary stenting)

It would take nearly 10 years to eliminate the frightening risk of acute or subacute stent thrombosis. A number of strategies were proposed; these included use of full-dose unfractionated heparin, low-molecular-weight heparin, dextran, sulfinpyrazone, aspirin, and antivitamin K. The combination of these drugs was ineffective and led to significant bleeding at the puncture site resulting in big hematomas that required vascular repair. In this context, although stenting was recognized to be effective for the treatment of abrupt periprocedural occlusion and to help avoid emergency bypass operations, many investigators were ready to abandon this technique for the treatment of restenosis. However, coronary stenting would be resuscitated by two new findings by Antonio Colombo from Italy and Paul Barragan from Marseille.

Antonio Colombo, through extensive use of intravascular ultrasound, demonstrated that in many cases, stent implantation was far from perfect, with malapposition and insufficient deployment. From these observations, he recommended inflation of the balloon at a higher level of pressure to improve embedding of the stent inside the wall. With a larger lumen and a better flow, stent thrombosis might be avoided.
Almost simultaneously, Paul Barragan reported that a dual antiplatelet treatment with aspirin and ticlopidine was successful.11 Barragan participated in a trial launched by Bertrand et al (The TACT trial [Ticlopidine Angioplasty Coronary Trial]). The goal of this trial was to verify if an antiplatelet drug (ticlopidine) could prevent restenosis. This study presented at the American Heart Association meeting in 1992 had negative results but was able to demonstrate the benefits of ticlopidine + aspirin in preventing acute periprocedural complications of balloon angioplasty. Thus, Barragan continued to use this dual anti-platelet treatment after completion of the study. In performing stent implantations, he was the only investigator to have no (or rare) cases of stent thrombosis. Finally, on the basis of a French registry collecting data on the usual strategies, it was observed that the combination of aspirin and ticlopidine was markedly effective for reductions in stent thrombosis and vascular complications.12 Three randomized studies performed initially in Europe13,14 and later in the United States15 demonstrated the benefit of this dual antiplatelet treatment (Figure 5). Subsequently, Bertrand et al showed that another thienopyridine (clopidogrel) was superior to ticlopidine (the CLASSIC trial [CLopidogrel Aspirin Stent International Cooperative study]).16

The danger of acute/subacute thrombosis having been overcome, the so-called “stentomania” began, with an increasing number of stent implantation procedures taking place.

**The fight against restenosis**

**The role of stenting**

In 1991, Serruys et al published in the New England Journal of Medicine the results from the first 105 patients in the world treated with the Wallsten.17 This report essentially addressed the problem of subacute thrombosis, but few readers overlooked the fact that the rate of restenosis after stenting was only 14%. In this context, Dutch investigators began a multicenter registry, and several investigators (Serruys, Bertrand, Rutsch) launched a randomized study assessing the role of coronary stenting in the treatment of restenosis. Although initially impossible to find support from industry for such a trial, the tenacity of Serruys, de Jaegere, Kiemeneij and colleagues led to the launch of the BENESTENT I trial (BEngel-Netherlands STENT) in Belgium and the Netherlands. This pilot study included only 60 patients and took almost 1 year to complete in four centers with a total number of almost 4000 interventions, demonstrating the skepticism of the interventional cardiology community for stenting.18 This landmark study demonstrated the benefit of coronary stenting for the treatment of restenosis. The results were confirmed by an American trial (STRESS [STent RESTenosis Study]).19 Later, the results were complemented by the BENESTENT II study, which was performed with a heparin-coated stent and showed that bleeding complications almost completely disappeared.20

However, over time, it appeared that in-stent restenosis was a true matter of concern. It was discovered that though the scaffolding role of stenting prevented negative remodeling—the shrinkage of the artery—as a reaction to the metallic foreign body, the vascular wall generated a new, intense hyperplasia. Solinas et al21 showed the different aspects of in-stent restenosis, as follows: in-stent restenosis was focal (margin or mid-stent) in 42%, diffuse in 22%, proliferative (ie, with extension beyond the stent) in 30%, and even occlusive in 6%. Several techniques were used to address this new problem; these included redilation by balloon (mainly for focal in-stent restenosis), by the stent-in-stent technique, by Rotablator therapy, and even by brachytherapy. At first glance, brachytherapy seemed promising but was subject to numerous regulations due to the rules of radioprotection. This method was never well accepted, was limited to a small number of centers, and was finally abandoned with the emergence of drug-eluting stents.

**Drug-eluting stents (the second revolution in coronary stenting)**

Over the years, several investigators—particularly Wim van der Giessen—attempted to coat the struts of the metallic stents with different substances, the goal being to coat the struts with a polymer as a drug-carrier vehicle; these drugs sought to inhibit the cell cycle. In July 1999, Cordis Corporation studied a stent coated with a polymer releasing the drug rapamycin. The company conducted a pilot study in Rotterdam, the Netherlands with Patrick Serruys and in Sao Paulo, Brazil with Eduardo Souza, in which 15 patients were studied with angiographic and intravascular ultrasound follow-up. The two principal investigators were surprised to discover that at 4 and 12 months’ follow-up there was no evidence of neointimal hyperplasia. These results led to a randomized clinical trial conducted in 237 patients treated by bare-metal stent or the Cypher, the first drug-eluting stent—the RAVEL study (RAndomized study with the sirolimus-eluting VElocity balloon-expandable stent in the treatment of patients with de novo na-
tive coronary artery Lesions).22 This study, presented at the European Society of Cardiology congress in Vienna (September 2001) by Marie-Claude Morice, was a new “turning point in coronary interventional cardiology,” as there was zero re-stenosis.

Subsequently, two major trials confirmed these excellent results: the SIRIUS trial (SIRolImus-elUting Stent in coronary lesions),23 as well as the TAXUS trial (Treatment of de novo coronAry disease using a single paclitaxel-elUting Stent),24 which used another eluting drug, paclitaxel. Later, the course of drug-eluting stents was disturbed by a frightening issue—at the 2006 European Society of Cardiology congress in Vienna, results suggesting late stent thrombosis were presented. Fortunately, these scary results were not confirmed,25 but they led to a still ongoing debate about the duration of dual antiplatelet treatment: 6 months, 12 months, or more? Nevertheless, the development of drug-eluting stents continued and with the new drug-eluting stents using a different drug-carrier vehicle, all of them have been shown to offer efficacy and safety.

Thus, the challenges were overcome: the cage prevents negative remodeling and the eluted drug prevents cell proliferation and migration (Figure 6). A final step was the development of stents that used biodegradable polymers and bioresorbable scaffolds: drug-eluting stents with biodegradable polymers provide the benefit of drug-eluting stents in the early days/months and of the bare-metal stents later. A number of prostheses were studied: AXXESS (Biosensors), Orsiro (Biotronik), DESyne (Elixir), Infinium (Sahajanand), Biomine (Meril Life).

As the polymer may induce side effects, polymer-free drug-eluting stents have been proposed. The eluting drug may be introduced into a microporous surface on metallic stents. Examples include the Yukon stent (Translumina), BioFreedom (Biosensors), VESTAsync (MIV Therapeutics), Nano (Xience), and Bicare (Lepu Medical). In other examples, the Optima stent (CID Vascular) proposes small reservoirs of tacrolimus covered with carbofilm, and the Amazonia PAX stent (MINVASYS) is a cobalt-chromium stent coated with paclitaxel.

Bioresorbable stents are very promising: they offer the vascular scaffold for a certain amount of time and then the implanted materials are progressively resorbed. This offers a number of advantages, including the elimination of foreign bodies inside the wall, restoration of endothelial coverage, and possibly restoration of vasmotion. These biodegradable stents can be divided into two categories: metallic stents that are magnesium based and those that are polymeric resorbable—more than 10 stents of this type have been studied, made of poly-L-lactic acid (PLLA) and poly-D,L-lactic acid. Absorb BVS (Abbott Vascular) is a fully resorbable stent which has obtained the CE mark (Conformité Européenne [European conformity]); the ABSORB II trial published in the Lancet in 2014 compared Absorb BVS vs the Xience metallic drug-eluting stent in a cohort of 501 patients.27-29 At follow-up, there was no significant difference in terms of safety and efficacy between the two devices. Currently, there is great interest for these new bioreabsorbable stents, but it is obvious that a longer follow-up is needed in order to reach final conclusions. There are currently a number of studies underway evaluating these new devices.

**Conclusion**

Coronary stenting represents one the most important advances in the field of coronary angioplasty. With this technique, percutaneous coronary interventions are safe in most cases and the risk for patients to be sent for surgery for emergency bailout procedures has become minimal. Additionally, the risk of reintervention after angioplasty is markedly reduced after drug-eluting stent implantation. With coronary stenting, coronary interventional procedures, as minimally invasive techniques, have become the primary method of myocardial revascularization in man. ■

**Keywords:** coronary stenting; interventional cardiology; myocardial revascularization; percutaneous coronary angioplasty
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