EDITORIAL
Stable angina: to stent or not to sent? ............................................... 2
Luis Henrique Wolff Gowdak (Brazil)

ORIGINAL ARTICLES
ORBITA and ISCHEMIA: what's the message? ..................................... 4
William E. Boden (US)

Fractional flow reserve: current evidence base in stable coronary artery disease .......... 9
Ozan M. Demir, Matt Ryan, Haseeb Rahman, Divaka Perera (UK)

Post-PCI angina: should I worry? ..................................................... 13
Luis Henrique Wolff Gowdak, Mario Marzilli (Brazil, Italy)

What is optimal medical therapy? .................................................. 17
Mario Marzilli, Maria Chiara Scali (Italy)

Trimetazidine in the era of PCI .................................................... 20
Olímpio R. França Neto (Brazil)

CASE REPORT
A patient with stable angina and mild ischemia: do I have the COURAGE not to stent the lesion? ......................................................... 24
Luis Henrique Wolff Gowdak (Brazil)

REFRESHER CORNER
Composite end points in cardiovascular clinical trials ................................ 28
Otavio Berwanger, M. Julia Machline-Carrion (Brazil)

HOT TOPICS
Choosing between functional and anatomical imaging for stable angina ............. 33
Aida Soufiani (Morocco)

GLOSSARY .................................................................................. 37
Gary D. Lopaschuk (Canada)
Stable angina: to stent or not to stent?

Luis Henrique Wolff Gowdak, MD, PhD, FESC
Laboratory of Genetics & Molecular Cardiology, Heart Institute, São Paulo, Brazil

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

We start our journey by reading the article by Prof. Boden about the messages two audacious clinical trials—ORBITA and ISCHEMIA—may have to share. For many years, cardiologists have accepted the concept that if there is angina and/or myocardial ischemia, there must be coronary stenosis. Therefore, treatment should be aimed at finding the lesion and fixing the artery by PCI if feasible. The already published and much discussed ORBITA trial adds to a list of previous clinical trials (COURAGE and BARI-2D, for instance) in which the benefit of PCI in patients with stable angina was very limited if present at all. The ISCHEMIA trial is eagerly awaited, to further enrich our knowledge about the prognostic impact of revascularization in stable patients with moderate-to-severe myocardial ischemia.

Another contribution from the cath lab is the determination of FFR (or fractional flow reserve) which, in theory, by providing a more physiological assessment of coronary stenosis, could be used to guide myocardial revascularization. Prof. Perera discusses this topic in his article and tells us about the principles and pitfalls of FFR, and how clinical trials based on FFR may have overestimated the benefits of FFR-guided revascularization in terms of hard endpoints.

As PCI became more widely used in patients with stable angina, the unexpectedly high rates of early recurrence or persistence of angina after PCI served as a reminder that stable angina is not a single disease, but rather a complex multifactorial pathophysiological...
process. Prof Marzilli and I present our thoughts on the subject, highlighting that, besides the high incidence, many PCIs in patients with stable angina are deemed inappropriate according to current guidelines and accompanied by an intrinsic risk of complications. Moreover, patients with post-PCI angina are at higher risk of cardiovascular events and represent an economic burden on the health care system.

If PCI ought to be offered to patients unresponsive to optimal medical therapy, Prof Marzilli returns to explain that any optimal medical strategy should follow a couple of principles, including a match between the main pathophysiological process related to myocardial ischemia and the mode of action of the selected antianginal drug; safety, tolerability, and lack of drug interactions should be considered; and the clinical profile/comorbidities of the patient acknowledged. He is urging us to have a more individualized approach to treating the patient with stable angina as opposed to the “one size fits all” approach.

Next, we learn from Prof França Neto that, if PCI is clearly indicated in a patient with stable angina, the cardiac cell should not be forgotten as a therapeutic target for protection using trimetazidine. This unique agent will, by shifting the production of ATP from the free-fatty acid oxidation pathway to the more efficient glucose oxidation pathway, reduce oxidative stress and membrane damage, reduce myocardial injury, reduce the occurrence/severity of post-PCI angina, and might favorably impact major adverse cardiac and cerebrovascular events in post-PCI patients.

Another task I was given in this issue was to share a clinical case of a patient with stable angina in which a decision had to be made between placing a stent or keeping the patient on optimal medical therapy as the most effective strategy for symptom control.

In the Refresher Corner, we invited Prof Berwanger to explain what the criteria are for composite end points in clinical trials and why they matter. As we follow more and more clinical trials being presented during medical meetings and/or published in highly respected journals, it is important that we try to fully understand the chosen end points because they will directly influence the interpretation of the main results of the trial and, as such, the potential clinical application of the new data being generated.

Finally, Prof Soufiani was invited to shed some light on the everlasting debate on choosing between functional and anatomical imaging in the assessment of a patient with stable angina, particularly at the initial evaluation.

I believe that the opening phrase of Hamlet’s soliloquy should invite us to pause for reflection before referring a patient with stable angina for PCI. If there’s no clear benefit in preventing death and/or myocardial infarction, and symptom-relief may be short-lived in patients with stable angina, I’d dare to say that more often than not we would choose “not to act.” But, in doing so, we must “act” to offer our patients the most effective combination of antianginal drugs and disease-modifying agents, tailored to the needs of each and every patient.

If I could have a word with Hamlet, I believe I know what I’d have to say to him… ■
Introduction

Since the advent of coronary angiography more than 60 years ago, the diagnosis and treatment of coronary artery disease (CAD) has been predicated on the plausible assumption that “significant” flow-limiting atherosclerotic obstructions of the epicardial coronary arteries are the proximate cause of both angina and myocardial ischemia.1 This paradigm has been proven in patients with an acute ST-segment elevation myocardial infarction (STEMI) with an occluded infarct-related coronary artery and in many high-risk patients with acute coronary syndromes (ACS) with a stenotic culprit coronary stenosis, where clinical benefit is derived from percutaneous coronary intervention (PCI). However, there is scant evidence that treating coronary obstructions in patients with chronic angina and stable ischemic heart disease (SIHD) reduces mortality and morbidity, despite the continued evolutions in stent design.
Thus, since the advent of PCI in 1977,² cardiologists have been imbued with the long-held belief of PCI superiority in stable CAD management and have continued to embrace a “PCI-first” approach, despite international professional society guidelines advocating for an optimal medical therapy (or “OMT-first”) approach. This somewhat monolithic and anatomically driven practice paradigm, however, has not been challenged, despite the existence of compelling evidence that many angina patients (both men and women) do not have significant flow-limiting epicardial coronary obstructions as the singular cause of their symptoms and objective findings of ischemia.³

Since PCI for SIHD is procedurally nearly identical to that performed for STEMI or ACS, many physicians have accepted the premise that PCI would confer a more durable clinical benefit (ie, beyond symptom relief) in SIHD patients with flow-limiting coronary stenoses. This assumption has been challenged and largely undermined by two major randomized clinical trials—COURAGE and BARI 2D.⁴,⁵ While neither study showed a reduction in death or death/myocardial infarction (MI) (follow-up periods, 5 to 7 years), both provided a compelling rationale for deferred revascularization and an up-front trial on OMT (ie, intensive pharmacotherapy, lifestyle intervention, and secondary prevention). Conversely, as an initial management strategy in patients with SIHD, PCI did not reduce death, MI, or other major cardiovascular events when added to OMT. These findings of strategic equivalence have now been observed to persist for up to 15 years.⁶

A more recent trial, the FAME-2 trial,⁷ undertaken in 888 patients randomized to fractional flow reserve (FFR)-guided (FFR ≤0.80) PCI plus OMT or to OMT alone, showed that the primary composite end point of death, MI, or urgent revascularization occurred in 4.3% in the PCI group and 12.7% in the OMT group (P<0.001), which was driven by a lower rate of urgent revascularization in patients assigned to PCI with OMT (1.6% vs 11.1%; P<0.001) during a relatively short (7-month) follow-up.⁸ Further analysis of the FAME-2 trial results showed that the principal benefit associated with the FFR-guided PCI approach was only a reduction in the rate of hospitalization for unplanned revascularization, while there was no significant between-group difference in the rate of death, MI, or the composite of death or MI. Even extending the follow-up of FAME-2 to 2 and 5 years did not change the lack of benefit of FFR-guided PCI on the “hard” clinical outcomes of death and/or MI.⁹,¹⁰ In fact, there were numerically more cardiac deaths at 5 years in the PCI group (n=11) vs the OMT group (n=7) (hazard ratio, 1.54; 95% CI, 0.60-3.98).⁹ In addition, two recent meta-analyses of more than 5500 SIHD patients who were randomized to PCI versus OMT showed no reduction in cardiovascular events for the end points of death, MI, hospitalization for ACS, and freedom from angina.¹¹,¹²

Despite the inability to demonstrate a salutary effect of PCI on even angina relief, most cardiologists still believe in the superiority of PCI for angina relief vs OMT, that is until the ORBITA trial, published in 2017, called this into question.¹³ The results of ORBITA were unexpected because no incremental benefit was observed for treadmill walking time, or any objective measure of angina relief and quality of life among those who underwent PCI vs those who received a blinded sham procedure, although, by design, ORBITA only had a 6-week follow-up.¹³ Nevertheless, for a small 200-patient cardiovascular outcomes trial, the impact of ORBITA has been both remarkable and profound. As the first sham-controlled trial of PCI in SIHD patients, all of whom had significant flow-limiting coronary stenoses (mean diameter stenosis, 84%), including an abnormal FFR (mean, 0.69), ORBITA was unable demonstrate an additive effect
of FFR-guided PCI on treadmill exercise duration, the frequency and severity of angina, or several quality of life indices.\(^{13}\) Considering that stenting a coronary artery with a mean 84% stenosis should have imparted an immediate clinical and physiologic benefit between treatment groups, even at 6 weeks, these provocative findings defied both expectations and conventional wisdom. One possible insight from ORBITA is that an interventional procedure that is expected to result in symptomatic improvement may, in part, be related to both the patient’s and physician’s belief that the procedure is therapeutically effective, which calls into serious question whether PCI has a truly definable therapeutic effect or whether the presumed benefit may, in part, be due to the patient’s inherent belief of benefit, which Rajkumar et al\(^{14}\) termed the “power of telling,” or the potential benefit of “faith healing.”

ORBITA was a rigorously designed and executed randomized trial that was undertaken using objective exercise and physiologic outcome measures before and after stabilization on OMT and well-validated quality of life metrics before and after randomization.\(^{13}\) However, there are well-recognized limitations, including:\(^{15}\)

- Small sample size
- Underpowered
- Unethical for subjecting subjects with significant flow-limiting CAD to a sham procedure (or deferred PCI for clinical need)
- Normal FFR in 28% to 32% of randomized patients (ie, no “physiologically significant,” flow-limiting stenosis at the time PCI was undertaken after OMT intensification)
- All patients had single-vessel CAD
- Short 6-week duration of follow-up that some critics believed was too brief to assess potential PCI benefit
- Intensity of OMT for 6 weeks prior to the planned PCI vs sham PCI randomization was too labor-intensive and “not real-world,” which was similar to the criticism that COURAGE encountered.\(^{4,13}\)

One common question persisting post–ORBITA has been whether these trial results will change clinical practice. The answer to this question is “likely no” because the narrative will be that rates of PCI for stable CAD are declining, while more recent data from a large American College of Cardiology national PCI registry show that, based on “appropriateness use criteria,” the percentage of patients undergoing “inappropriate PCI” (or “rarely appropriate PCI”) is likewise declining.\(^{16}\) However, what is not entirely clear at present is whether there has been an increase in “coding creep” to up-classify (or reclassify) CAD patients with “stable angina” to “unstable angina.”\(^{17}\) Since only a few states in the US mandate public reporting of PCI use and appropriateness data, which is both voluntary and not verified for accuracy or quality control, it is unclear how such data can be reliably ascertained and interpreted in the setting of an “honor system” without objective oversight.

What the results of ORBITA do show us, however, is that cardiologists also need to be honest about the fact that our biases and pre-existing beliefs of PCI may often color the way we approach this discussion with patients about the presumed benefits of PCI. For example, when even a stable CAD patient is found to have a flow-limiting coronary stenosis during angiography, what is frequently conveyed to the patient in the catheterization lab (along with the frightening visual image of a coronary angiographic obstruction or narrowing) is the potential for an impending catastrophic event: that is, if we don’t intervene and “fix this blockage” immediately, the risk of MI or death may occur. In this context, who could blame a patient for acquiescing to PCI? However, I suspect there is little discussion about the lack of PCI benefit on improved survival or reduced MI in the setting of the cardiac catheterization laboratory where the ease and convenience of undertaking ad hoc PCI is frequently compelling for the interventional cardiologist to attempt.\(^{18}\) The results of ORBITA, along with those of COURAGE,\(^{4,6}\) BARI 2D,\(^{5}\) and even FAME-2\(^{7,9}\) should teach us that we should provide our patients and their families with factual, transparent information about the risks and benefits of all CAD treatment approaches (eg, PCI, coronary bypass surgery, and OMT),\(^{19}\) and specifically, that we may now need to start informing our patients that PCI may not necessarily improve their angina—or that perhaps only a minority of patients may experience significant, durable angina relief.

However, an even greater reason why the results of ORBITA are unlikely to change contemporary clinical practice is that it remains unclear whether the extent and magnitude of myocardial ischemia in the setting of obstructive CAD is the principal driver of subsequent cardiac events—notably spontaneous (type 1) MI and the composite of MI and cardiovascular death. Neither COURAGE and BARI 2D explicitly
required that enrolled patients had to demonstrate moderate-to-severe ischemia on noninvasive testing, and, while all patients in COURAGE did have objective evidence of myocardial ischemia at baseline, most appeared to have mild-to-moderate ischemia. In addition, all the previous “strategy trials” comparing OMT with or without PCI were uniformly undertaken after the results of coronary angiography were known to the study investigators, which introduces the possibility that bias may have led to the decision not to randomize patients to OMT or PCI once the coronary anatomic results were apparent.

For these reasons, a large, multinational randomized trial, funded by the US National Institutes of Health, has been under way since 2012 to address these key (and yet unresolved) clinical questions. The ISCHEMIA trial (NCT01471522) has enrolled 5179 patients with multivessel CAD and objective evidence of at least moderate ischemia at baseline as assessed by stress echocardiography, treadmill exercise testing, myocardial perfusion imaging, or cardiac magnetic resonance imaging. Of note, all subjects with moderate-to-severe ischemia at baseline first undergo a blinded coronary computed tomography angiography assessment to exclude left main stem CAD and the absence of obstructive epicardial CAD, after which eligible patients are randomized to an invasive strategy of revascularization of choice (PCI with third-generation drug-eluting stents (DES) or coronary bypass surgery with OMT) or a conservative strategy of OMT alone, with coronary angiography and revascularization reserved only for OMT failure. The primary end point is a composite of cardiovascular death, nonfatal MI, resuscitated sudden cardiac death, or hospitalization for ACS or heart failure in a time-to-first-event analysis during an average 4.5-year follow-up. The ISCHEMIA trial is scheduled to conclude on June 30, 2019. Key secondary outcomes include quality of life and the composite end point of cardiovascular death or MI. It is anticipated that the results of the ISCHEMIA trial will inform clinical practice regarding the benefit of revascularization plus OMT versus OMT alone in a higher-risk population of SIHD patients than has been previously subjected to prospective study.

In summary, perhaps the time has come for a paradigm shift in how we view stable CAD. The results of trials to date have failed to show a conclusive benefit for PCI in SIHD patients concerning “hard” clinical outcomes. The results of ORBITA likewise tell us that even short-term angina relief may not be uniformly achieved in all patients despite successful stenting of high-grade coronary stenoses using DES guided by FFR. These findings suggest that we may need to expand our scientific thinking about the many causes and mechanisms of both angina and myocardial ischemia, particularly in stable CAD patients, and we need to uncouple the singular association between obstructive CAD and epicardial coronary revascularization, which is largely unsupported by rigorous trial data and evidence-based medicine. Angina and ischemia have many causes, and, until the results of the ISCHEMIA trial are published, both the evaluation and treatment of SIHD patients need to be tailored to the individual patient, with particular emphasis on the continued use and benefits of OMT.19

Disclosure/Acknowledgments: The author has no conflicts of interest to declare.

REFERENCES


Fractional flow reserve: current evidence base in stable coronary artery disease

Ozan M. Demir, MBBS; Matt Ryan, MBBS; Haseeb Rahman, MBBChir; Divaka Perera, MA, MBBChir, MD
NIHR Biomedical Research Centre and British Heart Foundation Centre of Excellence, School of Cardiovascular Medicine and Sciences, St Thomas’ Campus, King’s College London, UK
Correspondence: Prof Divaka Perera, Cardiovascular Division, Rayne Institute, St Thomas’ Hospital, London, SE1 7EH E-mail: Divaka.Perera@kcl.ac.uk

Abstract
The development of fractional flow reserve (FFR) has revolutionized interventional cardiology, leading to a physiology-based instead of anatomy-based approach to coronary revascularization. There have been three landmark FFR trials: DEFER, FAME, and FAME-2. In the DEFER trial an FFR threshold of 0.75 was used to guide revascularization; subsequently, in the FAME and FAME-2 trials the FFR threshold was increased to 0.80. All these studies demonstrated that FFR-guided revascularization resulted in improved clinical outcomes with reduction in major cardiovascular events. However, in the FAME and FAME-2 trials this reduction in major cardiovascular events has principally been driven by difference in rates of urgent revascularization. The treatment thresholds for FFR have increased from initial derivation studies where the threshold was 0.75. This has been in an empirical bid to increase the sensitivity and negative predictive value, at the inevitable cost of specificity; potentially to the detriment of hard end points. Recently, resting indices have been proposed. However, despite much interest there remain some unresolved questions including the discordance with FFR that occurs in 20% of patients. In conclusion, there is overwhelming evidence for the use of FFR in guiding percutaneous coronary intervention in stable coronary artery disease, and it has become a reference surrogate measure of ischemia. However, outcome data are principally driven by rates of urgent revascularization. It may be that a lower threshold is required, as suggested by early studies, to demonstrate a mortality benefit for FFR-guided revascularization.

Keywords: coronary physiology; fractional flow reserve; percutaneous coronary intervention

Introduction
The development of fractional flow reserve (FFR) has revolutionized interventional cardiology, leading to a physiology-based instead of anatomy-based approach to coronary revascularization. The seminal work by Pijls et al in 1996 demonstrated that FFR is a surrogate for ischemia testing at the point of diagnostic angiography.1 This led to a number of large randomized studies demonstrating that FFR-guided revascularization resulted in improved clinical outcomes for patients with coronary artery stenosis.2,3 Recently, resting pressure-wire indices (avoiding hyperemia) have been developed and validated against
This review provides a comprehensive overview of the evidence base for FFR, its use in the context of different coronary artery disease (CAD) pattern, and the role of emerging resting indices.

**Principles of fractional flow reserve**

In 1993, Piljs et al described the theoretical basis for the calculation of coronary flow reserve from coronary pressure, namely that the ratio of distal coronary to aortic pressure during maximal hyperemia in a stenosed coronary artery was linearly and strongly correlated with flow in the diseased artery in relation to hypothetical flow in an entirely disease-free artery supplying the same myocardial territory. This was a landmark step as pressure measurements are markedly easier to perform than coronary flow measurements in clinical practice. In 1996, the optimal FFR threshold for detecting ischemia was established as 0.75; at sensitivity of 88%, specificity 100%, positive predictive value 100%, negative predictive value 88%, and diagnostic accuracy of 93%.1

There have been three landmark FFR trials: DEFER,8 FAME,2 and FAME-2.3 In the DEFER trial, patients with moderate coronary artery stenosis were divided into three groups: (i) patients with FFR >0.75 were randomly assigned to either defer group (n=91) where no percutaneous coronary intervention (PCI) was performed; (ii) or perform group (n=144) where PCI was performed; (iii) patients with FFR <0.75, reference group (n=144), underwent PCI. At 5 years, event-free survival was similar between the defer and perform groups (80% and 73%, respectively; P=0.52). Furthermore, the risk of myocardial infarction or cardiac death in patients with an FFR value ≥0.75 stenosis was <1% per year, and not decreased by stenting.8 In the FAME trial, 1005 patients with multivessel CAD were randomized to FFR-guided or angiography-guided PCI. FFR-guided PCI, with a higher threshold of ≤0.80 for PCI, resulted in a reduction in the per-patient number of stents (2.7±1.2 versus 1.9±1.3, P<0.001). At 1 year the composite MACE-orientated primary end point (death, nonfatal myocardial infarction, and repeat revascularization) was 18.3% in the angiography group and 13.2% in the FFR group (P=0.02). However, despite FAME demonstrating that an FFR-guided PCI results in better clinical outcomes, this was principally driven by the repeat revascularization.

In the FAME-2 open-label trial, patients in whom at least one stenosis was functionally significant (FFR≤0.80) were randomly assigned to FFR-guided PCI plus optimal medical therapy (PCI group) or optimal medical therapy alone (medical-therapy group). In addition, patients in whom all stenoses had an FFR > 0.80 were entered into a registry; this represented approximately one third of patients enrolled in the study. The study was halted prematurely due to significant difference in the primary end point 4.3% in the PCI group versus 12.7% in the medical therapy alone group, P<0.001; this was mostly driven by a lower rate of urgent revascularization in the PCI group than in the medical-therapy group (1.6% versus 11.1%; P<0.001).3 However, urgent revascularization was performed following diagnosis of unstable angina on clinical assessment alone in half these patients, without any cardiac enzyme or electrocardiogram abnormalities. Furthermore, neither the rate of death from any cause nor the rate of myocardial infarction differed significantly between the PCI group and the medical-therapy group. Nonetheless, at 5 years, the rate of the primary end point was lower in the PCI group than in the medical-therapy group (13.9% vs 27.0%, P<0.001). The difference was again driven by urgent revascularizations, which occurred in 6.3% of the patients in the PCI group as compared with 21.1% of those in the medical-therapy group.9

Of note, whilst the FAME and FAME-2 trials have been positive, demonstrating significantly lower MACE rates, this has been principally driven by difference in rates of urgent revascularization. The treatment threshold for FFR has increased from initial derivation studies where the cutoff established was 0.75, to 0.80 in the FAME studies.10 This has been in an empirical bid to increase the sensitivity and negative predictive value of both these indices, at the inevitable cost of specificity; potentially to the detriment of hard end points including mortality.11 This has been further illustrated by the IRIS-FFR registry, which included >8000 lesions, suggesting the optimal FFR threshold cardiac death or myocardial infarction was 0.64.12 At present, the COMFORTABLE prospective study is recruiting to investigate the superiority of medical therapy plus PCI over medical therapy alone in reducing major cardiovascular events in patients presenting with coronary stenosis with “gray zone” FFR values, between 0.75 and 0.80.13
Evidence for FFR in different lesions

Whilst the evidence base for FFR has been established, its utility in different CAD lesion subsets remains a topic of interest, especially as interventional cardiologists seek to physiologically assess increasingly complex patterns of CAD. The vast majority of the clinical outcome data for FFR have been derived from isolated lesions in single or multiple vessels. Herein, we outline role of FFR in serial stenoses and chronic total occlusions, both commonly encountered during diagnostic coronary angiography.

Serial stenoses

The clinical utility of FFR in vessels with multiple stenoses is hampered as one stenosis influences the FFR of the others and complicates the determination of FFR of each individual stenosis. However, studies have demonstrated that FFR may be measured accurately in serial stenoses. In a prospective study, 131 patients with serial intermediate stenoses, pullback pressure-wire to the ostium of the coronary artery under steady-state hyperemia was performed and the stenosis that caused the largest pressure step-up (“primary target lesion”) was treated first. After PCI to the “primary target lesion” repeat FFR was performed, leading to further PCI in only 26 vessels (18.4%). The primary limitation of this method is that, due to interplay between lesions, the operator may inadvertently perform PCI on the lesion that is actually less significant in the first instance. More recently, it has been demonstrated that this error is significantly improved using a mathematical correction model, incorporating routinely available pressure-wire pullback data.

Chronic total occlusions

In patients with chronic total occlusion there is usually blood supply to that vessel distally via collateral vessels. In these circumstances, it is thought that assessment of FFR in the donor vessel may lead to erroneously positive FFR values. However, it is important to appreciate that FFR measurements remain valid but incorporate the effect of a given stenosis on both coronary territories supplied. Hence, if the chronic total occlusion is treated the FFR rises, due to reduction in the dependent myocardial volume. A recent study showed that FFR values increased from 0.78 to 0.81 (P=0.001) following treatment of the occluded vessel.

Acute coronary syndromes

In the setting of acute coronary syndromes, assessment of the non-culprit vessel with FFR, performed at the time of intervention to the culprit vessel, is affected by abnormalities of epicardial vasomotor tone and microvascular tone. This phenomenon in the non-culprit vessel is transient. Hence, whilst it may be efficacious to perform FFR measurements in the acute setting, it is preferable that this is performed at a later setting to allow these physiological abnormalities to normalize. Conversely, assessment of the culprit vessel with FFR in the setting of an acute coronary syndrome is not recommended, as there is sparsity of any robust data on the efficacy of FFR.

Non-hyperemic physiological indices

Over the last decade there has been significant interest in the ratio of distal coronary to aortic pressure, at prespecified segments of the cardiac cycle, without the use of hyperemia. Instantaneous flow reserve (iFR), measured in the latter 75% of diastole, is the most commonly utilized resting index. Patients managed on the basis of a dichotomous iFR threshold of 0.89 were found to have equivalent rates of major adverse outcomes to those managed on the basis of a FFR threshold of 0.80 in two large RCTs: DEFINE-FLAIR and iFR-SWEDE-HEART. Recent ESC guidelines have made a class I recommendation for physiological assessment of coronary disease by either FFR or iFR when planning revascularization in stable CAD. However, there remain some unresolved concerns about iFR, including the difficulty in ensuring a consistent resting state in patients undergoing invasive coronary assessment and the discordance in classification based on dichotomous FFR and iFR thresholds that occurs in 20% of patients. Other resting coronary indices, such as whole-cycle Pd/Pa ratio or the Pd/Pa ratio at different phases of the cardiac cycle, have been shown to be very similar to iFR, both numerically and with respect to their agreement with FFR, with a diagnostic accuracy compared with FFR of 76% to 77% for resting indices including iFR.
Conclusions

There is overwhelming evidence for the use of FFR in guiding PCI in stable coronary artery disease, and it remains the reference standard ischemia test. Despite this, uptake has been suboptimal. Whether the advent of practically simpler but potentially less accurate approximations of FFR might increase physiological assessment of CAD remains unclear. Furthermore, whether these indices can be applied to more complex patterns of disease needs systematic evaluation. Finally, the gray zone between deferral and treatment thresholds needs further exploration and is particularly pertinent in the face of mounting evidence that revascularization may be of limited prognostic benefit in stable CAD.

Disclosure/Acknowledgments: The author has no conflicts of interest to declare.

REFERENCES


Post-PCI angina: should I worry?

Luis Henrique Wolff Gowdak, MD, PhD, FESC; Mario Marzilli, MD, PhD

Laboratory of Genetics & Molecular Cardiology, Heart Institute, São Paulo, Brazil (Luis Henrique Wolff Gowdak); Cardiovascular Department, University of Pisa, Pisa, Italy (Mario Marzilli)

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

Abstract: Percutaneous coronary intervention (PCI) has become one of the commonest procedures in cardiovascular medicine, with an estimated 480 000 inpatient PCI procedures performed in the United States in 2014. In patients with acute coronary syndromes, particularly those at higher risk (patients with STEMI, diabetes, older individuals), PCI significantly impacted outcomes if performed in a timely fashion. On the other hand, the role of PCI in patients with stable angina is still being revised as medical therapy continues to evolve both for better symptom control as well as for more effective secondary prevention. In patients with hemodynamically significant coronary stenosis in the presence of limiting angina or angina equivalent and who are unresponsive to optimal medical therapy, PCI should be considered. Still, post-PCI angina will occur in as many as one-third of all patients in the first year following PCI with stent implantation for stable symptoms. The main mechanisms implicated in post-PCI angina include residual disease or disease progression, diffuse atherosclerosis, or microvascular dysfunction. Post-PCI patients with angina are at higher risk of future cardiovascular events and represent an economic burden.

Heart Metab. 2019;78:13-16

Keywords: angina; myocardial ischemia; percutaneous coronary intervention; prognosis

Introduction

Percutaneous coronary intervention (PCI) has become one of the commonest procedures in cardiovascular medicine. According to the latest report from the American Heart Association, an estimated 480 000 inpatient PCI procedures were performed in the United States in 2014. Nevertheless, the rate of any cardiac stent procedure declined by 27% between 2006 and 2009 after rising by 61% from 1999 to 2006.

What to expect from PCI in patients with coronary artery disease

In patients with acute coronary syndromes, particularly those at higher risk (patients with ST-elevation myocardial infarction [STEMI], diabetic patients, older individuals), PCI significantly impacted outcomes if performed in a timely fashion. In a meta-analysis published by Huynh et al including 23 randomized controlled trials (RCTs—8140 patients) and 32 observational studies (185 900 patients), primary PCI compared with fibrinolytic therapy was associated with short-term reductions in mortality, reinfarction, and stroke in patients with STEMI. In patients older than 75 years old with STEMI, primary PCI led to lower rates of heart failure, mechanical complications, and cardiac arrest compared with fibrinolysis. The European Society of Cardiology Guidelines on the Management of Acute Myocardial Infarction in patients presenting with ST-segment elevation states that “a primary PCI strategy is recommended over fibrinolysis within indicated timeframes” (class I, LOE A).
On the other hand, the role of PCI in patients with stable angina is still being revised as medical therapy continues to evolve both for better symptom control as well as for more effective secondary prevention. For instance, in the 1980s, myocardial revascularization would confer greater benefit for angina control compared with pre-optimal medical therapy (MT). Figure 1 shows the impact of angina control conferred by revascularization (CABG and/or PCI) compared with MT with different periods of follow-up in selected clinical trials performed in the last 35 years. We can easily see that MT, if performed adequately, has increasingly rendered more patients free of angina.

Consequently, as of today, PCI has an indication in relieving symptoms in patients with hemodynamically significant coronary stenosis in the presence of limiting angina or angina equivalent, who are unresponsive to optimal MT. For definition purposes, a hemodynamically significant coronary stenosis is assumed in the presence of documented ischemia or FFR ≤0.80 (or iwFR ≤0.89), or >90% stenosis in a major coronary vessel. Therefore, an adequate referral for PCI in patients with stable angina should be based on a triad of: (i) symptoms (limiting angina), (ii) optimal MT; and (iii) the presence of ischemia and/or high-grade coronary stenosis.

Unfortunately, these recommendations are seldom followed by cardiologists worldwide. Borden et al., using the CathPCI Registry and the Dartmouth Atlas data, assessed the use of antianginal drugs in more than 300,000 elective PCIs for stable coronary artery disease (CAD); they found that one third of all patients referred for an elective PCI were taking no antianginal medications, whereas only 19% were taking at least two antianginal drugs before PCI. In another study involving more than 500,000 PCIs performed in the United States between the years 2009 and 2010, the appropriateness of the indication for PCI was compared in patients with acute (71.1%) or nonacute indications (28.9%). For acute indications, 98.6% of all PCIs were classified as appropriate, whereas for nonacute indications, only about half (50.4%) were classified as appropriate. The majority of inappropriate PCIs for nonacute indications were performed in patients with no angina (53.8%), low-risk ischemia on noninvasive stress testing (71.6%), or suboptimal (≤1 medication) antianginal therapy (95.8%).

Moreover, even if significant coronary stenosis is found, the link between the coronary stenosis being the cause of angina may be elusive, as previously described by Marzilli et al. We should acknowledge that the presence of atherosclerotic, obstructive lesions in patients with stable angina is just one element in a complex multifactorial pathophysiological process. Persistent inflammation, microvascular dysfunction, endothelial dysfunction, and altered vasomotor tone may all contribute to myocardial ischemia, alone or...
in combination. Therefore, it should not come as a surprise that the removal of the stenosis by PCI may not completely abolish symptoms, as many patients will have recurrence or persistence of symptoms afterward, as many as one third of all patients in the first year following PCI with stent implantation for stable symptoms; conversely, many patients with coronary stenosis will be free of angina if managed medically. Table I shows the main mechanisms implicated in recurrence/persistence of angina post-PCI.

<table>
<thead>
<tr>
<th>Structural</th>
<th>Functional</th>
</tr>
</thead>
<tbody>
<tr>
<td>Residual disease or disease progression</td>
<td>Epicardial coronary spasm</td>
</tr>
<tr>
<td>In-stent restenosis/in-stent thrombosis</td>
<td>Microvascular dysfunction</td>
</tr>
<tr>
<td>Diffuse atherosclerosis</td>
<td></td>
</tr>
<tr>
<td>Intramyocardial bridge</td>
<td></td>
</tr>
<tr>
<td>Coronary dissection</td>
<td></td>
</tr>
</tbody>
</table>

Contrary to PCI performed in the acute setting, PCI in patients with stable angina still has to prove that it can favorably impact clinically significant end points such as mortality and/or myocardial infarction. A recent meta-analysis comprising 5 RCTs and 8117 patients looked at the long-term outcomes of PCI versus MT in patients with stable CAD. They found that, at a mean follow-up of 5 years, PCI was not associated with a reduction in cardiovascular outcomes, angina relief, or survival benefit compared with MT.

Risks associated with PCI

To determine the net clinical benefit of PCI in stable patients (ie, the sum of the change in expected benefits minus the change in expected risks as a result of treatment), we must assess the risks associated with PCI, especially periprocedural myocardial infarction and contrast-induced acute kidney injury (CI-AKI). In the contemporary era of interventional cardiology, the risk of in-hospital mortality following PCI increased from 0.8% in 2004 to 2.1%. Periprocedural MI during PCI occurs in approximately 3% to 6% of patients and up to one third of patients have evidence of procedural myocardial injury. More than a laboratory abnormality, several studies have demonstrated that periprocedural MI is associated with an increased risk of morbidity and mortality.

It is believed that CI-AKI may occur in more than one third of patients undergoing coronary angiography or PCI, depending on risk factors such as compromised baseline glomerular filtration rate (GFR), advanced age, reduced LVEF, diabetes, and contrast media volume. In a recent study comprising 980 patients undergoing coronary angiography or PCI, Andreis et al showed that CI-AKI was the strongest predictor of 8-year cardiovascular adverse events (threefold increased risk), and cardiac death (sevenfold increased risk).

Besides its clinical significance, post-PCI angina also imposes an economic burden on the health care system. In a multipayer administrative claims database, 51 710 patients underwent PCI between 2008 and 2011 and were followed for up to 36 months. Post-PCI angina or chest pain was present in 28% by 12 months and 40% by 36 months of the study population. Compared with patients who did not experience chest pain, angina or ACS, total health care costs in the first year after the index PCI was 1.8 times greater for patients with angina or chest pain (US$32,437 vs US$17 913; P<0.001).

Prognosis of patients with post-PCI angina

In the same study, 12 months after index PCI, patients with post-PCI angina or chest pain had more hospitalizations, medical visits, and diagnostic tests including five times more cardiac catheterizations, and six times more stress tests. It is worth mentioning that the mean and median times to angina or chest pain after the index PCI were approximately 4 months and 2.5 months, respectively.

Conclusions

PCI for patients with stable angina has a role in providing (although it may be short-lived) symptom relief for those patients who are truly refractory to optimal MT. It will not impact clinical outcomes such as mortality or myocardial infarction. The evidence-based benefits of PCI for stable CAD are rarely presented by physicians, and some implicitly or explicitly overstated its benefits. If we consider CAD not as a single clinical entity but rather as a syndrome with a multifactorial origin and different underlying physiological mechanisms, we may then appreciate post-PCI angina as a failure either to recognize that coronary stenosis was not the cause of angina.
or that another mechanism is now causing angina, despite the removal of the stenosis, in the case of a patent stent. In other words, a risky and costly procedure may have been inadequately indicated and performed. Post-PCI patients with angina are at higher risk of future cardiovascular events and represent an economic burden.

Should we worry about post-PCI angina? Based on the above, we absolutely think so!

Disclosure/Acknowledgments: Dr Gowdak has received lecture fees and travel expenses from Servier for lectures given at international conferences.

REFERENCES

What is optimal medical therapy?

Mario Marzilli MD, PhD; Maria Chiara Scali, MD, PhD
Cardiovascular Department, University of Pisa, Pisa, Italy
Correspondence: Prof Mario Marzilli, Viale dei pini 293 A, 56019 Pisa, Italy
E-mail: mario.marzilli@med.unipi.it

Abstract: While the enthusiasms triggered by revascularization procedures in chronic ischemic syndromes are fading, medical therapy is regaining a central role in the management of this condition. The latest guidelines from both sides of the Atlantic recommend medical therapy as the initial management and stress the need for either “maximal” or “optimal” or, more recently, “guideline-dictated” medical therapy, which should include one or two antianginal agents. The limitations of these recommendations in this era of growing awareness of the multifactorial nature of myocardial ischemic syndromes are briefly summarized. ■ Heart Metab. 2019;78:17-19

Keywords: guideline dictated medical therapy (GDMT); optimal medical therapy (OMT); trimetazidine

Treatment of any medical condition is aimed at prolonging patients’ survival and at improving quality of life. The efficacy of any medical (or surgical) therapy should be established with regard to its effects on these two parameters. These elementary concepts are not so obvious when it comes to treatment of chronic myocardial ischemic syndromes. The first point is that, as of today, no treatment has been conclusively shown to improve mortality and/or morbidity in chronic ischemic syndromes.1 So we cannot look at survival as a ranking parameter among possible treatments, nor can we promise patients that they will live longer with any treatment. In practice, to identify the “best possible,” if not the “optimal,” therapy, we can rely only on quality of life, survival being of little, if any, help.

Acceptance of quality of life as the primary target of treatment has several relevant implications. Quality of life is not always easy to assess, even applying established scoring systems, like the Seattle Angina Questionnaire, because angina perception may be influenced by factors not directly related to ischemia severity and/or duration, including social, economic, psychological, and environmental conditions.2 Therefore, it does not directly express treatment efficacy. Moreover, the precipitating mechanisms of ischemia may change in time or overlap, modifying the response to treatment.3

Recently, “chronic myocardial ischemia” is being perceived more and more as a lifelong condition, that will require lifelong treatment. This new perception calls for greater attention to the side effects and clinical tolerability of drugs. It is quite obvious that, if the primary goal of treatment is to help patients to live a better life, agents that, in the long run, may worsen the quality of life (because of depression, fatigue, constipation, erectile dysfunction, etc) should be avoided. So, in the definition of “optimal medical therapy,” not only efficacy but also tolerability and lack of serious side effects become relevant.

Current guidelines have given conflicting recommendations, shifting from “optimal” to “guideline-dictated” medical therapy.3 When the word “optimal” was used, the implication was that therapy should include “one to two antianginal” medications in order to be “optimal.” It is difficult to accept this statement, purely based on the number of prescribed drugs, with no consideration of the efficacy in ameliorating patients’ symptoms.
Apparently, the more recent trend to recommend “guidelines-dictated” medical therapy should be easier to follow, were it not for the major limitations of this approach.

Most current guidelines propose a ranked list of antianginal medications, identifying first-line agents and second-line agents. To further complicate medical decisions, guidelines admit that there are circumstances where the second-line agents can become first-line.3

This approach has been recently challenged, based on the following observations:

1. In these therapeutic recommendations there is no effort to match the mechanism of action of the antianginal agent with the precipitating mechanism of myocardial ischemia. This is even more surprising in guidelines that acknowledge the multifactorial nature of chronic ischemic syndromes, which can be associated with fixed or dynamic stenosis, with focal or diffuse coronary vasospasm, with microvascular dysfunction, and possibly with other, not yet well understood mechanisms.3,4

2. These recommendations do not consider the clinical profile of the patients who, more and more often, present comorbidities that can contraindicate some of the “first-line” agents: hypertension, diabetes, peripheral vascular disease, depression.5

3. These recommendations do not appear to be evidence-based. In a recent analysis of published trials over the last 50 years, no superiority emerged for any of the agents listed as first-line versus those listed as second-line.6,7

It must be admitted, however, that most studies have major methodological limitations, because patients were enrolled independently of the pathogenetic mechanism of angina and this may explain why no superiority has ever emerged. In a more focused approach it is easy to predict that, eg, Ca-channel blockers would prove more effective and better tolerated than β-blockers if tested in a cohort of patients with vasospastic angina.5 And most published trials focus exclusively on short-term efficacy, with limited if any data on long-term clinical tolerance. Probably, none of the two “first-line” agents would compare with trimetazidine in microvascular angina, in angina in patients without significant coronary obstructions, etc.9

In addition, none would match trimetazidine in clinical tolerability in any patient subset. However, head-to-head comparisons have not been performed, and probably never will.

In addition, the ESC Guidelines distinguish between antianginal agents and “disease-modifying agents.”3 The second group includes aspirin, ACE inhibitors, and statins. Given the space limits of this manuscript, we will not discuss this second group, where the only novelty are recent data challenging the protective role of aspirin, and we will focus on the concepts that can help in prescribing the “best possible antianginal therapy.”

How do we define the “best possible” treatment strategy for a patient with chronic myocardial ischemia? Once a clinical diagnosis of angina pectoris (as distinct from chest pain) has been established, a number of sequential steps should be considered.10

Based on a careful history-taking, clues as to the precipitating mechanism should be sought. When angina is easily predictable, being consistently associated with physical exercise, at a relatively constant workload, the presence of a severe stenosis as the main culprit for the symptoms is highly probable. Conversely, angina occurring in an unpredictable fashion and in the absence of any identifiable precipitating cause suggests functional factors.11,12 Microvascular angina can be induced by exercise, but the threshold is highly variable and it is not associated with regional contractile dysfunction at echostress.13-15

In summary, right after the diagnosis of angina pectoris an effort is required to identify the most likely precipitating mechanism as a condition to wisely choose the best antianginal agent. Next, a detailed assessment of the cardiovascular system must be conducted to identify factors that can be useful in the choice of the best drug, such as heart rate, LV function, arterial pressure, etc. Lastly, attention must be paid to comorbidities.16 With the progressive aging of angina patients, most of them suffer from systemic comorbidities, the most frequent being hypertension, diabetes mellitus, chronic obstructive pulmonary disease, and peripheral arterial disease. Putting together these three levels of information, a tailored choice for the antianginal medication can be made. Treatment should be started as soon as possible, ie, as soon as this information has been made available, and prolonged over time. Repeated checks for efficacy, patient compliance, absence of side effects, and possible changes in the pathogenesis of the ischemic syndrome, must be planned.
Following these steps, the efficacy and tolerability of life-long medical therapy can be substantially improved (Table I). Admittedly, this is just an effort to be consistent with the new understanding of myocardial ischemic syndromes, and it is not based on scientific evidence, because there is very little evidence available, and it appears unlikely that we will have new trials in this area in the foreseeable future. But, this effort is inevitable, giving that alternative approaches, including PCI, still have to prove their superiority over medical therapy, and given that in the largest fraction of angina patients an invasive approach cannot be considered, either because no coronary obstructive lesion is found at angiography or because, if found, it is not amenable to revascularization.17

Table I Steps from the diagnosis of angina pectoris to the best possible medical therapy.

1. Identification of the precipitating mechanism(s) of angina
2. Profiling the patient’s cardiovascular system
3. Diagnosing systemic comorbidities
4. Assessing patient’s tolerance and side effects
5. Programmed checks for efficacy, side effects, angina mechanism

Conclusion

The growing awareness that myocardial ischemia can be precipitated by multiple mechanisms, and that these mechanisms may overlap in the same patient and may change in time, mandates a tailored approach to drug choice in chronic myocardial ischemic syndromes. An effort should be made in each patient to identify the mechanism responsible, to assess the global cardiovascular status, and to consider the comorbidities in order to identify the most appropriate drug combination.

Disclosure/Acknowledgments: The authors have no conflict of interest to disclose.

REFERENCES

Introduction

Ischemic heart disease is the major cause of death and disability worldwide, except in the lowest-income countries. Angina pectoris, the most frequent clinical presentation of ischemic heart disease, increases progressively in its prevalence among adults aged 40 years and older, ranging from 4% to more than 11%. Angina not only affects quality of life, but it is also associated with an increased risk of cardiovascular events.

Percutaneous coronary intervention (PCI) is a vital strategy for managing obstructive coronary artery disease. Lifestyle management, control of risk factors, guideline-directed medical therapy, and myocardial revascularization are the recommended therapies for patients with ischemic heart disease. However, despite contemporary treatments, angina remains a debilitating problem. Large clinical trials consistently indicate that many patients present persistent symptoms or signs of myocardial ischemia, even with guideline-directed medical therapy and revascularization; in some studies, this proportion varies from 25% to 35%. Restenosis, coronary atherosclerosis progression, and incomplete revascularization provide reasons for the recurrence of symptoms in a percentage of patients even after successful PCI. At the same time, functional causes, such as vasomotor abnormalities of epicardial coronary arteries and/or coronary microvascular dysfunction, could provide a justification for symptoms in the other patients.

In addition, PCI may also induce coronary spasm or endothelial cell injury and the debris from atherosclerotic plaques or thrombi may cause coronary artery distal embolization, thereby leading to myocardial ischemia or myocardial injury. Peri- and postprocedural myocardial injury or necrosis play an essential prognostic role after PCI.

Abstract: Guideline-directed medical therapy and coronary revascularization by percutaneous coronary intervention (PCI) are important approaches to treating patients with ischemic heart disease. However, even after PCI and with guideline-directed medical therapy, a significant percentage of patients still present with angina. In addition, PCI can also induce myocardial ischemia, myocardial injury, and reperfusion injury. Trimetazidine, an anti-ischemic agent widely used for the treatment of coronary artery disease, has cytoprotective actions that could protect against ischemia and reperfusion injury in patients undergoing PCI. Several trials have shown that trimetazidine improves left ventricular ejection fraction and reduces elevated cardiac troponin levels, angina attacks, and ischemic ST-T changes on the electrocardiogram in patients undergoing PCI. Moreover, the use of trimetazidine in patients submitted to revascularization results in an improvement in exercise stress test parameters, such as time to ischemic ST-segment depression, time to onset of angina, and exercise test duration, as well as a reduction in the weekly number of angina attacks and nitrate consumption. This article will review the effects of trimetazidine on patients submitted to percutaneous coronary interventions.

Keywords: ischemic heart disease; metabolic protection; percutaneous coronary intervention; trimetazidine
Lastly, reperfusion injury is a pathophysiological phenomenon that occurs because of damage to the myocardium after restoring blood flow after a certain period of coronary occlusion. The production of oxygen free radicals caused by reperfusion of an ischemic heart can lead to damaged cardiac cells. PCI can cause a transient ischemia of the myocardium, leading to metabolic changes, including disturbances in the electrical activity and contractility of myocardial cells associated with hemodynamic disturbances.13

**The effects of trimetazidine**

Trimetazidine is an anti-ischemic agent commonly employed as part of the treatment for coronary artery disease. It works by inhibiting the long-chain mitochondrial 3-ketoacyl coenzyme A thiolase, and gives a stimulus to pyruvate dehydrogenase, which leads to a change in cardiac energy metabolism from fatty acid oxidation to glucose oxidation. As a result, trimetazidine has cytoprotective properties, providing a reduction in myocardial cell acidosis and calcium overload, preservation of intracellular ATP levels, an increase in the antioxidant capacity, and protection against oxygen free radical–induced toxicity.5,14,15

Trimetazidine favorably alters the level of oxidative stress markers. In the study by Iskesen et al,14 it increased the level of superoxide dismutase and glutathione peroxidase (major antioxidant enzyme systems that limit intracellular accumulation of oxygen free radicals during normal aerobic metabolism) and decreased the level of malondialdehyde (end product of lipid peroxidation). Trimetazidine also reduces membrane damage induced by reactive oxygen species and protects tissue from free radicals with its antioxidant effects.16,17 These effects are particularly useful in the reperfusion period. Some experimental studies have shown that trimetazidine can prevent a sharp increase in the permeability of mitochondrial membranes, decreasing the rate of cardiomyocyte apoptosis.18,19

Several clinical trials have shown that trimetazidine significantly improves left ventricular ejection fraction, reduces elevated cardiac troponin levels, angina attacks, and ischemic ST-T changes on the electrocardiogram in patients undergoing PCI.20-24 Polonski et al performed an open, randomized clinical trial (RCT) that assessed the effect of pretreatment with trimetazidine on the degree of ischemia during PCI. The intervention group (n=22) received oral trimetazidine as a pretreatment. The mean ST-segment elevation during all balloon inflations was significantly lower in the trimetazidine group than in the control group (-1.66±1.50 mm vs 3.29±1.59 mm, P=0.001). Similarly, the maximal amplitude of the T-wave alterations was 4.50±2.90 mm with trimetazidine vs 9.25±4.97 mm in control patients (P=0.0005). Angina and rhythm disturbances were more frequent in the control group.20

The effect of preprocedural acute oral administration of trimetazidine on PCI-induced myocardial injury was evaluated by Bonello et al in 266 patients with stable angina pectoris and single-vessel disease undergoing PCI. Before the intervention, patients were randomly distributed to one of two groups. One group received a loading dose of 60 mg of trimetazidine, while the other group did not receive this loading dose. Postprocedural cTnI levels were significantly reduced in the trimetazidine group at all time points (from 6 hours to 24 hours).21

In the study by Chen et al in 101 patients with stable or unstable angina pectoris who were randomized to either the trimetazidine (n=54) or the control (n=47) group before PCI. Prior to coronary angiography, one group was given oral trimetazidine, 20 mg three times a day for 5±2 days in addition to a loading dose of 60 mg 30 minutes before PCI. The dosage each day was maintained for 4 weeks postprocedure. No patient in the trimetazidine group presented with angina during the procedure; however, 12 patients (25.5%) in the control group presented with angina (P<0.001). The trimetazidine group showed fewer changes in the ST-segment and T wave during balloon dilatation in the PCI procedure (60.8% vs 78.3%; P<0.05). Four weeks after the PCI, the trimetazidine group presented with a higher ejection fraction (66.6±7.1% vs 63.0±7.7%; P=0.03). See ref 22 for further details.

Xu et al examined the effect of trimetazidine on recurrent angina pectoris and left ventricular structure in elderly patients with multivessel coronary heart disease and diabetes mellitus after drug-eluting stent implantation. Seven hundred patients with coronary heart disease undergoing coronary angiography were randomized to receive trimetazidine or placebo after being treated with a drug-eluting stent. During the 2-year follow-up, the incidence (P=0.024) and sever-
ity of angina was significantly improved in the trimetazidine group (n=255), in addition to silent myocardial ischemia (P=0.009) and angina pectoris–free survival (P=0.011).24

Zhang et al performed a meta-analysis of randomized controlled trials to evaluate the effect of trimetazidine on patients undergoing PCI. Nine studies involving 778 patients were included. Additional use of trimetazidine significantly improved left ventricular ejection fraction and reduced elevated cardiac troponin Ic level, angina attacks during PCI, and ischemic ST-T changes on the electrocardiogram during PCI. Additional use of trimetazidine for patients undergoing PCI may reduce myocardial injury during the procedure and improve cardiac function (Figure 1).22

Furthermore, according to different trials, recurrent angina affects one-third to one-fifth of patients submitted to a successful PCI within a 1-year follow-up.8-11 The subgroup analysis of the Trimpol II study showed that the addition of trimetazidine to metoprolol in symptomatic patients with a history of revascularization for coronary artery disease (PCI or coronary artery bypass grafting) resulted in a significant improvement in time to 1-mm ST-segment depression (385.1±144.6 seconds vs 465.0±143.8 seconds; P<0.01), exercise test duration (466.9±144.8 second vs 524.4±131.5 second; P=0.048), total workload, and time to onset of angina. The weekly number of angina attacks and nitrate consumption were also significantly reduced in the trimetazidine group when compared with placebo.25

The incidence of stent restenosis has risen as more patients are being treated with drug-eluting stents. Chen et al evaluated, in 768 patients who underwent PCI with drug-eluting stents, whether treatment with long-term trimetazidine reduced the incidence of stent restenosis. The trimetazidine group 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-treated patients also presented with a higher left ventricular ejection fraction than control patients (65.4±10.7% vs 63.1±10.4%; P=0.006).26

Finally, we look forward to seeing the ATPCI trial results, a new international, phase 3 study evaluating the clinical impact of adding a metabolic agent to post–PCI angina treatment. ATPCI is a multicenter, randomized, double-blind, placebo-controlled study in patients treated with trimetazidine for 2 to 4 years. ATPCI, which stands for “EfficAcy and safety of Trimetazidine in Patients with angina pectoris having been treated by percutaneous Coronary Interventions,” will encompass 6007 patients from 27 countries up to 30 days after PCI. The primary efficacy end point of ATPCI is the time to the first occurrence of: (i) cardiac death; (ii) hospitalization for a cardiac event; (iii) recurrent or persistent angina that results in the addition, switching, or the increase of the dose of one of the evidence-based antianginal drugs; and (iv) recurrent or persistent angina, leading to a coronary angiography. The primary safety end point is the incidence of serious emergency adverse events with trimetazidine.27

**Figure 1** Effects of trimetazidine on patients undergoing PCI.
Conclusion

In summary, trimetazidine is a metabolic agent that protects the heart from ischemic damage and oxidative stress. In patients with stable angina undergoing revascularization, trimetazidine may prevent reperfusion injury and damage to cardiac cells, improve left ventricular function, and reduce angina and electrocardiographic ischemic changes during PCI. It can also improve exercise stress test parameters and reduce angina episodes after revascularization. The ATP-PCI trial should contribute to a better understanding of the benefits of trimetazidine in patients with angina pectoris treated by percutaneous coronary interventions.

Disclosure/Acknowledgments: The author has no conflict of interest to disclose.

REFERENCES

A patient with stable angina and mild ischemia: do I have the COURAGE not to stent the lesion?

Luis Henrique Wolff Gowdak, MD, PhD, FESC
Laboratory of Genetics & Molecular Cardiology, Heart Institute, São Paulo, Brazil

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

Abstract: For many years, physicians worked on the assumption of a linear, straightforward link: angina ⇒ myocardial ischemia ⇒ coronary stenosis; therefore, it also seemed straightforward that to treat angina, we should tackle the culprit element, coronary stenosis, by fixing it with a stent. Advances in our understanding of the complex, multifactorial process leading to myocardial ischemia allowed us to appreciate that coronary stenosis is just one among many elements concurring to provoke myocardial ischemia. Moreover, clinical trials that challenged the “PCI-first approach” in the management of patients with stable angina demonstrated unequivocally that, for patients with nonlimiting symptoms, a run with a combination of antianginal drugs and disease-modifying agents could be safely offered before considering a myocardial revascularization procedure. Based on those premises, we present a clinical case that highlights the role of optimal medical therapy (OMT) in the management of a patient with stable angina as the initial therapeutic strategy as opposed to immediate PCI strategy. ■ Heart Metab. 2019;78:24-27

Keywords: angina; treatment; coronary artery disease; trimetazidine; myocardial revascularization; angioplasty

Introduction

This issue of Heart & Metabolism focuses on the subject of coronary stenting in patients with stable angina according to current guidelines and the most recent trials. For many years, physicians worked on the assumption that there was a linear, straightforward link connecting angina ⇒ myocardial ischemia ⇒ coronary stenosis, and that therefore, it was also straightforward that to treat angina, we should tackle the culprit element, coronary stenosis, by fixing it with a stent. Thus, coronary stenosis ⇒ percutaneous coronary intervention (PCI) with stent implantation ⇒ angina relief and prognostic benefit. A careful read of this issue should enlighten us and help us see this from a different perspective.

Advances in the understanding of the complex, multifactorial process leading to myocardial ischemia have allowed us to appreciate that coronary stenosis is just one among many elements concurring to provoke myocardial ischemia, clinically translated as angina and/or myocardial dysfunction in stable patients. Moreover, clinical trials that challenged the “PCI-first approach” in the management of patients with stable angina demonstrated unequivocally that, for patients with nonlimiting symptoms, a run with a combination of antianginal drugs and disease-modifying agents...
could be safely offered before considering a myocardial revascularization procedure. The role of PCI in improving symptoms has been further challenged with the publication of the ORBITA trial. But even before that, in FFR-guided PCI compared with medical treatment, as in the FAME-2 trial, the rate of clinically significant end points such as death or myocardial infarction was not affected by PCI.

Based on these premises, we present a clinical case that highlights the role of optimal medical therapy (OMT) in the management of a patient with stable angina as the initial therapeutic strategy as opposed to immediate PCI strategy.

**Clinical presentation**

A 70-year-old woman was seen for recently diagnosed stable angina. She had a history of stage I hypertension, type 2 diabetes mellitus, and hypercholesterolemia for which she was taking perindopril-arginine 10 mg od, indapamide 1.5 mg od, rosuvastatin 20 mg od, metformin XR 1 g od, and empagliflozin 25 mg od. Six months before seeking medical attention, she noticed exertional angina during her morning walks, especially if uphill, quickly relieved by resting. Three months later, angina appeared to have progressed, because even walking two blocks on level ground would cause chest discomfort; just 1 week prior to her first appointment with a GP, during an argument with her daughter, prolonged angina occurred at rest and troubled her. When first seen, her heart rate (HR) was 76 bpm and BP 132/70 mm Hg. Physical examination was unremarkable. A resting ECG revealed mild left ventricular hypertrophy. Lab assessment and an echocardiogram were ordered; the patient was advised to start using the Angina Control app (from Servier) to record angina attacks by logging them and filling in the conditions associated with their onset (at rest or during effort) and whether or not nitroglycerin was required for relief. Aspirin (100 mg od) was added.

One month later, she attended with the results of the lab tests and the echocardiogram, as well as the number of angina attacks. The echocardiogram revealed a normal-sized heart with preserved left ventricular (LV) function (LV ejection fraction [EF] = 56%), concentric remodeling (LV mass index = 95g/m² and a relative wall thickness of 0.49), and hypokinesis of the lateral wall. Metoprolol succinate (50 mg od) was added.

On her next appointment, she was slightly better, with a decrease in the number of angina attacks and better exercise tolerance, although angina was still worrisome to her. She avoided social engagements and a long-awaited overseas trip was postponed. She was feeling fatigued but with no shortness of breath. HR dropped to 68 bpm and BP to 126/66 mm Hg. At this point, her GP referred her to see a cardiologist.

At her first appointment with the cardiologist, medication was not changed and a myocardial perfusion scan with dipyridamole stress was ordered. She returned another month later, and the cardiac scintigraphy revealed stress-induced ischemia in the anterior wall of the LV (extension 7%), a fixed perfusion defect in the mid- and apical portions of the inferolateral wall with a globally preserved LV function (LVEF = 50%). Invasive coronary angiography was ordered (Figure 1).

![Figure 1](image.png)

**Figure 1** Upper panel shows the left coronary artery system with left circumflex (LCx) occlusion (red arrow) and a 70% stenosis (white arrows) in the mid-portion of the left anterior descending coronary artery (LAD). On the right, we can see a 40% stenosis in the mid-portion of the right coronary artery (RCA).

<table>
<thead>
<tr>
<th>Laboratory tests</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>13.2 g/dL</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>39%</td>
</tr>
<tr>
<td>Glucose level</td>
<td>116 mg/dL</td>
</tr>
<tr>
<td>Hba1c</td>
<td>7.1%</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>153 mg/dL</td>
</tr>
<tr>
<td>LDL-cholesterol</td>
<td>76 mg/dL</td>
</tr>
<tr>
<td>HDL-cholesterol</td>
<td>40 mg/dL</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>185 mg/dL</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.9 mg/dL</td>
</tr>
<tr>
<td>GFR</td>
<td>66 mL/min/1.73 m²</td>
</tr>
</tbody>
</table>

**Table I** Results of selected laboratory tests.
What should be done now?

All major guidelines agree that a myocardial revascularization procedure should be pursued for improving symptoms and/or prognosis (Figure 2). The Heart Team convened and, although PCI with drug-eluting stent (DES) or coronary artery bypass graft (CABG) were both technically feasible, decided to further optimize medical treatment.

The patient was already on a β-blocker at the time a cardiologist assessed her and still complaining of angina with demonstrable stress-induced myocardial ischemia. Among the many options available as add-on therapy, there was a firm recommendation by the Heart Team to add trimetazidine. The patient was well medicated with disease-modifying agents including a high-intensity statin, an antiplatelet agent, and an ACE inhibitor; blood pressure and heart rate were adequately controlled and there was a fear of increasing the adverse effects (such as fatigue) with an increased dose of β-blocker. Moreover, recent studies have raised concerns about an increased risk of death with the use of β-blockers in patients with diabetes and coronary artery disease. Therefore, the choice of trimetazidine, an anti-ischemic agent free of any significant hemodynamic effect, was based on the available evidence of clinical benefit in terms of decreasing the number of angina attacks and the need for short-acting nitrates, increasing exercise tolerance and improving quality of life; additionally, the use of trimetazidine is usually safe and well-tolerated, with no known major drug interactions, including in patients with diabetes and/or heart failure.

The patient was informed about the results of the coronary angiography and the benefits/risks of leaving her on OMT, instead of referring her immediately to revascularization, to which she fully consented. Therefore, and because glomerular filtration rate was above 60 mL/min/1.73m², trimetazidine 35 mg bid was started on top of metoprolol, and she continued to use the Angina Control app.

Figure 2 shows the decrease in the number of angina attacks before treatment, after the β-blocker was started, and after trimetazidine was added. When last seen, she was free of angina, having experienced only two angina attacks in the previous month during a more brisk walk in the park on a cold morning. This individual response was also found in a large trial in which the use of trimetazidine on top of any antianginal background (including monotherapy with a β-blocker) provided a fast and significant decrease in the number of weekly angina attacks and improvement in the quality of life, including in patients with newly diagnosed angina.

If we look carefully at the indications for myocardial revascularization in patients with stable angina,

<table>
<thead>
<tr>
<th>Reports</th>
<th>Reports</th>
<th>Reports</th>
<th>Reports</th>
</tr>
</thead>
<tbody>
<tr>
<td>WEEK</td>
<td>MONTH</td>
<td>YEAR</td>
<td>WEEK</td>
</tr>
</tbody>
</table>

![Angina Control® app showing the number of angina attacks during 4 months of follow-up of a patient with a recent diagnosis of stable angina and the impact of medical treatment.](image_url)
we have to consider whether a procedure should be indicated to improve prognosis and/or to relieve angina. For the former, this patient does not fit into any major criteria in which evidence favors the intervention, like LM disease >50%, multivessel disease in the presence of LV dysfunction, or large (>10% LV) area of ischemia; so, we are left to consider revascularization for better symptom control.

However, the guidelines stated quite clearly that revascularization should be considered in the presence of limiting angina with insufficient response to optimized medical therapy, which is by far not the case. So, I believe the Heart Team chose wisely to not recommend revascularization as the initial therapeutic strategy.

**Conclusion**

In conclusion, in this newly diagnosed patient with stable angina with multivessel disease (with no proximal LAD disease), nonlimiting angina, preserved LV function, although myocardial revascularization either by PCI or CABG was feasible, OMT with a combination of a conventional antianginal agent (β-blocker) with a non-BP lowering agent such as trimetazidine provided excellent control of angina and increase in exercise tolerance, with good tolerability and no side effects.

**Disclosure/Acknowledgments:** Dr. Gowdak has received lecture fees and travel expenses from Servier for lectures given at international conferences.

**REFERENCES**

Why do we use composite end points?

The randomized clinical trial is considered as one of the major advances in medicine in the last century, and represents the gold standard for establishing the efficacy of cardiovascular therapies.

Results from large-scale trials have established practice-changing advances in cardiovascular medicine, such as reperfusion strategies in myocardial infarction, use of potent antithrombotic therapy, lipid-lowering therapies, blood pressure control, and newer antidiabetic drugs. These therapies have dramatically improved cardiovascular disease mortality rates over the past decades. On the other hand, the current lower mortality rates have provided increasing challenges for clinical trialists, as smaller incremental benefits from novel therapies would require studies with larger sample sizes and longer follow-up.

The statistical power of a randomized controlled trial is directly related to the number of events observed. The larger the number of events observed, the larger the statistical power. In the 1970s and 1980s, it was possible to conduct trials using all-cause mortality as the primary end point (such as trials comparing aspirin and placebo or fibrinolytic with placebo in patients with myocardial infarction). Currently, if one aims to design a trial with all-cause mortality as the primary end point, depending on the included patient characteristics, a trial would require a sample size of over 50 000 patients and several years of follow-up in order for a minimal number of events to accrue. One potential solution to overcome unfeasible sample sizes is to increase the number of observed events by using composite end points.

Composite (or combined) end points (or outcomes) in which two or more end points are combined are commonly used in contemporary cardiovascular clinical trials. This approach is often used in order to improve statistical efficiency and also to capture the overall effect of therapies in clinical trials. However, the correct interpretation of composite end points may be challenging for some physicians.

Interpretation of composite end points

The use of composite end points may lead to a misleading interpretation of results if the individual end points (components) differ in clinical relevance, if the frequency between components is different, and if the effect sizes differ markedly across the individual
components. Thus, when the gradient of importance for patients is large, and the more important components are less frequent and show small or non-clinically relevant treatment effects, use of composite end points can be misleading (Box 1).

**Box 1 Criteria for an appropriate composite end point.**

1. The components of the composite end point of similar importance to patients
2. The event rates for the components of the composite end point occur with similar frequency
3. The effect sizes for the components of the composite end point are of similar magnitude

In this sense, the components of a composite end point should be of similar clinical relevance and importance to patients. For example, in a trial in which the primary end point is composed of cardiovascular mortality, nonfatal myocardial infarction, or nonfatal stroke, all the components are clinically relevant and important to patients. This is a typical end point used in trials of acute and chronic coronary artery disease, as well as in cardiovascular prevention trials. Conversely, in a trial which uses a composite end point of cardiovascular mortality, nonfatal myocardial infarction, nonfatal stroke, need for revascularization, or stent thrombosis, the components are not of equal clinical relevance and importance to patients. Despite being an important variable to be measured, need for revascularization, for example, is not directly related to the natural history of the disease and may carry a component of medical decision or bias. Thus, it cannot be considered as having the same importance to patients as a fatal event such as cardiovascular mortality or a disabling stroke. The larger the difference in clinical relevance between the most and least important component end points, the larger our skepticism about the appropriateness of the composite end point.

In addition, in the case where the authors have found a statistically significant result in the primary composite end point, if the more important component occurs with far less frequency (lower event rates) than the less important ones, the difference may be due to the less important component. In this case, the composite end point becomes less informative. Finally, it is vital to evaluate not only the results in terms of the primary composite end point but also to evaluate the results in terms of the individual components. In this sense, if the magnitude of effects (effect sizes) varies between the individual components, the clinical implication of the results is also problematic.

The HOPE trial represents a classic example of adequate usage of composite end points. In this trial, 9297 high-risk patients who had evidence of vascular disease or diabetes plus one other cardiovascular risk factor and who were not known to have a low ejection fraction or heart failure were randomly assigned to receive ramipril (10 mg once per day orally) or matching placebo for a mean of 5 years. The primary outcome was a composite of myocardial infarction, stroke, or death from cardiovascular causes. Thus, all the components were clinically relevant. The frequency of the components was also consistent. Moreover, the authors found a 22% statistically significant relative risk reduction of the primary end point, but equally found consistent results with regard to the individual components (26% relative risk reduction of cardiovascular mortality, 20% relative risk reduction of myocardial infarction, and 32% relative risk reduction of stroke).

**Composite end points in the medical literature**

Systematic reviews have assessed the frequency and appropriateness of the use of composite end points in clinical trials. Freemantle et al assessed the incidence and quality of reporting composite end points in clinical trials published in major journals such as Annals of Internal Medicine, BMJ, Circulation, Clinical Infectious Diseases, Journal of the American College of Cardiology, JAMA, Lancet, New England Journal of Medicine, and Stroke from 1997 through 2001. The authors were able to find 167 original reports of randomized trials (with a total of 300 276 patients) that included a composite primary outcome that incorporated all-cause mortality. Sixty-three trials (38%) were neutral both for the primary end point and the mortality component. Sixty trials (36%) reported significant results for the primary outcome measure but not for the mortality component. Only 6 trials (4%) were significant for the mortality component but not for the primary composite end point, whereas 19 trials (11%) were significant for both. Twenty-two trials (13%) were inadequately reported.

Another systematic review assessed specifically cardiovascular trials published in the Lancet, Annals of Internal Medicine, Circulation, European Heart Journal, JAMA, and New England Journal of Medicine,
from 1 January 2002 to 30 June 2003. Of 114 identified randomized controlled trials that included a composite end point of importance to patients, 68% (n=77) reported complete component data for the primary composite end point; almost all (98%; n=112) primary composite end points included a fatal end point. Of 84 composite end points for which component data were available, 54% (n=45) showed large or moderate gradients in both importance to patients and magnitude of effect across components. When analyzed by categories of importance to patients, the most important components were associated with lower event rates in the control group (medians of 3.3 to 3.7% for fatal, critical, and major outcomes; 12.3% for moderate outcomes; and 8.0% for minor outcomes). Components of greater importance to patients were associated with smaller treatment effects than less important ones (relative risk reduction of 8% for death and 33% for components of minor importance to patients).

A more recent study reviewed four leading general/cardiology journals (Circulation, JAMA, The Lancet, and New England Journal of Medicine) from January 1, 2011 to December 31, 2016 and identified 140 trials with a cardiovascular composite end point as their primary result. The median number of components in the composite end point was 3, with 36.5% of those based solely on the combination of mortality, MI, or stroke (23 of 63 three-component composite end point trials). The inclusion of revascularization (rather than stroke) in the composite end point was also quite common (22 of 63 three-component composite end point trials). All but 12 trials included death, arguably the least ambiguous and most important end point, with the remaining components comprising nonfatal clinical events, and the need for, or outcomes of, procedures.

Taken together, these systematic reviews suggest that the use of composite end points is generally inadequate, given that higher event rates and larger treatment effects associated with less important components may lead to result in misleading interpretations of trial results.

**Future directions in the use of composite end points**

Several authors are proposing a rethinking and a reappraisal of composite end points in cardiovascular clinical trials (Box 2). A summary of some of the proposed solutions is presented below. A detailed discussion of the methodologies is beyond the scope of this narrative review.

1. Establish a consensus of event definitions, including recommended composite end points for each major cardiovascular area (heart failure, coronary artery disease, hypertension, etc).
2. Harmonize adjudication criteria between trials
3. Use weighting scheme methods
4. Perform analysis based on total number of events

**Box 2 Future directions in the use of composite end points in cardiovascular trials.**


For trials with similar design and objectives, it would be desirable to establish a consensus that would provide more homogeneity of common components within composite end points across trials. It would also be very important that the definitions used to adjudicate the events are similar between trials. These would facilitate trial interpretation and also would enable better conduct of systematic reviews and meta-analysis of such trials.

Another potential solution would be to differentially weight the components of a composite end point. For example, a stroke characterized by transient arm paresis does not have the same relevance as one resulting in disabling persistent hemiplegia. Similarly, a myocardial infarction defined by a small troponin rise would carry a much lower risk than a much larger one complicated by heart failure. Similarly, equal treatment in the analysis of fatal and nonfatal events may be misleading. Thus, further refinement of weights within an event type (ie, the weighting of the weights) and use of weighting or a ranking scheme in time-to-all-event approach to primary analysis represent potential solutions. Several methods have been proposed to achieve this.

Finally, in most cardiovascular trials, the analysis is based on time to first adjudicated event. Nevertheless, analytic methods based on a total number of events or recurrent events may better inform clinical practice.
Disclosure/Acknowledgments: Dr Berwanger has received grants and personal fees from AstraZeneca, Bayer, and Novartis; personal fees from NovoNordisk and Server; nonfinancial support from AstraZeneca; and educational support from Boehringer Ingelheim. Dr Machline-Carrion has received research grants from Amgen and personal fees from Boehringer Ingelheim.

REFERENCES

Choosing between functional and anatomical imaging for stable angina

Aida Soufiani, MD
Cardiology department, LNLCMCV, Ibn Sina University Hospital, Rabat, Morocco

Abstract: The choice of the best noninvasive imaging test for patients with stable angina is a topic of heated debate. Although the US and European guidelines continue to base the diagnostic approach on the use of pretest probability and then mainly functional imaging, the National Institute for Health and Care Excellence guidelines committee has put the anatomical imaging strategy based on computed tomography coronary angiography at the forefront. This strategy could even have a prognostic impact according to recent randomized trials. However, it should not be forgotten that, when confronted with a multifactorial disease, a single approach should not be used. In addition, when we place the patient at the center of our strategy, the choice of the imaging test often becomes self-evident. ■ Heart Metab. 2019;78:33-36

Keywords: diagnostic strategy; stable angina; coronary artery disease; functional testing; anatomical imaging; guideline; prognosis

Prologue

Monday morning, the last patient in the outpatient clinic, a 47-year-old man and active smoker:
- “Hello Doctor, for the past few months I’ve had chest pain when I walk fast. My wife thinks that I need to have an exam of my heart’s arteries...”
- “Well, let’s see.”

(Pros: It is tempting to perform invasive coronary angiography [ICA] directly, since prior stratification with functional testing failed to identify coronary artery disease [CAD] in large registries.1)
Cons: Apart from severe coronary lesions or extensive ischemia, revascularization performed in patients with chronic ischemic heart disease [IHD] has a limited impact on prognosis.2 Moreover, the ORBITA study proved that revascularization did not improve symptoms.3)
- “Let’s do a noninvasive test first,” I answer.

Introduction

Chronic stable angina is traditionally related to obstructive CAD. Therefore, as a symptom-based approach alone is not discriminatory,4 noninvasive testing is used at the initial presentation of patients with suspected angina to improve diagnostic rates of CAD, using ICA as a reference method. There is an ongoing debate between using functional or stress testing to induce ischemia (including ECG stress testing, stress echocardiography, myocardial perfusion imaging [MPI] with single-photon emission computed tomography [SPECT] or positron emission tomogra-
Abbreviations

CAD: coronary artery disease; CMR: cardiac magnetic resonance; CTCA: computed tomography coronary angiography; ICA: invasive coronary angiography; IHD: ischemic heart disease; MPI: myocardial perfusion imaging; ORBITA: Objective Randomised Blinded Investigation with optimal medical Therapy of Angioplasty in stable angina; PET: positron emission tomography; PROMISE: PROspective Multicenter Imaging Study for Evaluation of chest pain; PTP: pretest probability; SCOT-HEART: Scottish COmputed Tomography of the HEART; SPECT: single-photon emission computed tomography.

Functional or anatomical imaging for stable angina?

An ideal test?

The ideal tool must avoid unnecessary ICA by detecting low-risk patients, but it must also assess the prognosis of high-risk patients and influence subsequent decision-making to reduce cardiovascular events. Cardiovascular risk associated with the presence of coronary atheroma is proportional to its extent and its ischemic repercussions.

Functional tests all have similar typical sensitivities and specificities, approximately 85%, for the imaging and quantification of ischemia – apart from ECG stress testing – although CMR perfusion and PET have recently been shown to be the most accurate.

CTCA allows an assessment of the coronary lumen with an extremely high sensitivity when compared with ICA, as well as atherosclerotic plaque characterization, including measurement of coronary inflammation. Data on the diagnostic performance of SPECT and CTCA in direct comparison revealed a higher sensitivity of CTCA, which resulted in greater accuracy, except for patients with high calcium scores or high-risk anatomy. However, two recent direct comparative studies on the assessment of functionally significant CAD showed better performances for CMR-MPI and the highest accuracy for PET compared with CTCA.

Guidelines point of view

According to US and ESC guidelines, the diagnostic approach to stable CAD is based on a pretest probability (PTP) assessment and then on offering non-invasive testing to patients with an intermediate PTP. CTCA can be performed in patients with low-intermediate probability (<50%). In the PTP range (65% to 84%), functional imaging is required. The authors recommend considering the following for choosing an imaging method: (i) the patient’s resting ECG, physical ability to perform exercise, preferences, and comorbidities; (ii) contraindications to each test; (iii) availability of local resources (expertise and equipment); and (iv) the degree of exposure to radiation.

In contrast to this approach, the updated 2016 National Institute for Health and Care Excellence guidelines have removed the PTP model and recommend the use of CTCA 64 slice (or higher) as the first-line investigation in all patients with atypical or typical angina symptoms.

New evidence since the guidelines?

The debate between the two strategies continues to drive studies, especially comparative effectiveness trials aiming to improve CAD prognosis.

The PROMISE trial enrolled 10 003 patients with intermediate PTP scores from USA and Canadian centers to determine whether an initial assessment of suspected stable CAD using CTCA reduces major adverse cardiovascular events. After a 2-year follow-up, there was no improvement in death or myocardial infarction (MI) in a direct comparison with a functional-guided strategy (HR, 1.04; 95% CI 0.83-1.29).

A meta-analysis showed that, although the CTCA strategy is associated with significantly fewer MIs than the standard functional stress test, it also leads to significantly more invasive coronary procedures, without an overall reduction in mortality or cardiac hospitalizations.

The SCOT-HEART trial recruited 4146 patients who had been referred for stable chest pain and randomly assigned to CTCA plus standard care or standard care alone. After a follow-up of almost 5 years, CTCA plus standard care was associated with a significant reduction in nonfatal MIs vs standard care alone (HR, 0.60; 95% CI, 0.41-0.87; P=0.007),
which appears to be “attributable to better targeted preventive therapies and coronary revascularization.” We should emphasize that SCOT-HEART was a trial of CCTA plus stress testing vs stress testing alone; therefore, the benefit is linked to the combination of the two strategies. On the other hand, considering the standard “number needed to treat” for aspirin and statins (ie, 50 to prevent 1 death/nonfatal MI), it is somewhat surprising that 33 events could be reduced in the CCTA arm when just 97 more patients received preventive therapies. The small number of events observed can make the trial susceptible to the influence of chance or patients lost to follow-up, in addition to possible event coding bias related to whether it was an open-label trial with nonblinded event adjudication.

It makes sense that a strategy combining functional and anatomical imaging, like CCTA and CT MPI or CTCA FFR, or even a hybrid technique (SPECT/CT, PET/CT, and PET/MRI), improves CAD diagnostic accuracy, as well as the assessment of hemodynamically significant stenosis. However, further studies are needed to target the best overall approach to IHD for improving prognosis.

Epilogue

In a country like mine, with fewer than 10 CCTA/CMR/MPI centers per 36 million inhabitants (versus 9 CCTA centers per million in the UK and 19 in Germany) and where the cost of a CTCA or MRI is equivalent to an ICA, ie, 4 times that of exercise echography, an extremely rational diagnostic approach is needed. My patient had moderate ischemia in the LAD territory on exercise echocardiography; while he was waiting for funding for his ICA, he became completely asymptomatic on medical therapy.

Conclusion

In the same way that the pathophysiology of angina is multifactorial, its diagnosis cannot be reduced to any single “best” imaging test. Imaging of “functional” CAD at the level of the microvasculature, as was done in a recent study using T1 mapping in MRI, should spark more interest. Furthermore, if we refocus the debate around the patient, taking into account his clinical context, comorbidities and contraindications, as well as the availability and cost of each technique in addition to the local expertise; the choice of the imaging test often becomes self-evident.

Disclosure/Acknowledgments: The author has no conflict of interest to disclose.

REFERENCES


Contrast-induced nephropathy (CIN)
Contrast-induced nephropathy (CIN), is also referred to as contrast-induced acute kidney injury. CIN represents a serious form of renal injury that can arise from the intravascular administration of contrast media utilized in angiographic procedures (eg, coronary angiography, percutaneous coronary intervention). CIN is defined as an absolute (0.5 mg/dL) or relative (>25%) increase in serum creatinine 48 to 72 hours following the exposure to contrast agents compared with baseline serum creatinine values, when alternative explanations for impairment of renal function have been excluded.

Cardiac troponin I (cTnI)
Cardiac troponin I (cTnI) is a cardiac-specific regulatory protein that is involved in controlling the calcium-mediated interaction between actin and myosin. The measurement of cTnI is highly sensitive and specific for identifying cardiac muscle damage, and is accepted as a standard biochemical marker for the diagnosis of myocardial infarction.

Fractional flow reserve (FFR)
Fractional flow reserve (FFR) is the ratio of maximum blood flow in the presence of a stenosis to the maximal blood flow elicited in response to maximal pharmacological vasodilation/hyperemia (eg, in response to adenosine). FFR is a lesion-specific index of stenosis severity that can be calculated via the simultaneous measurement of mean arterial, distal coronary, and central venous pressures.

Glutathione peroxidase
Glutathione peroxidase is a peroxidase found in cells that helps to prevent lipid peroxidation of the cell membrane. The function of glutathione peroxidase is to reduce lipid hydroperoxides to their corresponding alcohols and to reduce free hydrogen peroxide to water.

Instantaneous flow reserve (iFR)
Instantaneous flow reserve (iFR) is an index used to assess the severity of coronary artery stenosis. iFR is calculated by measuring the resting pressure gradient across a coronary lesion during the portion of ventricular diastole when microvascular resistance is low and stable. In contrast to FFR, iFR can be determined without the need to administer vasodilatory/hyperemic agents (eg, adenosine).

Malondialdehyde
Malondialdehyde is a small molecule that is released from larger molecules, such as lipids, during oxidative stress. Measurement of the release of this compound is often used as an index of the degree of free radical oxidative stress to which a cell or organ is being exposed.

Open-label trial
An open-label trial is a type of clinical trial in which both researchers and patients are aware of the treatment/intervention being administered.

Oxidative stress
Oxidative stress in general is the deterioration in normal redox state primarily due to an imbalance between pro-oxidants and antioxidants sufficient to induce modification/damage of macromolecules. This results in the production of peroxides and free radicals that are often toxic to cells via damaging DNA, lipids, and proteins.

Oxygen free radicals
Oxygen free radicals are oxygen groups that have an unpaired electron. These oxygen free radicals are unstable and can react with lipids, proteins, or DNA and RNA, which can result in tissue damage.

Pd:Pa ratio
The Pd:Pa ratio represents the resting distal coronary pressure to aortic pressure ratio, and is an index of the hemodynamic significance of a coronary artery stenosis.

Periprocedural myocardial infarction
Periprocedural myocardial infarction is the development of a myocardial infarction during revascularization procedures, as revascularization procedures that involve direct instrumentation and manipulation of the coronary vasculature (eg, coronary bypass graft surgery) can predispose the myocardium to ischemic events and cause myocardial necrosis.

Pretest probability
Pretest probability is the probability of the presence of a condition (eg, disease) in an individual prior to the diagnostic test.
Sham procedure
A sham procedure is often used as the control/placebo surgery where everything entailing the surgical procedure is performed, except the step that mediates the end outcome. For example, ligation of the left anterior descending (LAD) coronary artery is often utilized in preclinical studies to mimic a myocardial infarction, and the sham surgery mimics every step of the actual surgery, except that the suture used to ligate the LAD coronary artery is simply threaded underneath the vessel and then removed, versus being knotted to occlude the vessel.

Superoxide dismutase
Superoxide dismutase is an antioxidant enzyme that counteracts high levels of superoxide free radicals (O₂⁻) by catalyzing the conversion of superoxide into either molecular oxygen (O₂) or hydrogen peroxide (H₂O₂).

T1 mapping
T1 mapping is a noninvasive cardiac magnetic resonance imaging technique that can be performed with or without contrast and is useful in characterizing myocardial tissue properties such as increased extracellular volume in conditions like hypertrophic cardiomyopathy and aortic stenosis. It can also noninvasively detect myocardial fibrosis.

Thiolase
Thiolase is an enzyme that breaks down either fatty acids or ketone bodies into acetyl CoA for the Krebs cycle. In the oxidation of fatty acids, 3-ketoacyl CoA thiolase shortens the fatty acid by two carbons (e.g., stearoyl CoA to palmitoyl CoA + acetyl CoA) via releasing acetyl CoA from the fatty acid, whereas in ketone body oxidation, acetoacetyl CoA thiolase breaks down acetoacetyl CoA into two molecules of acetyl CoA.