Original Article

Heart Metab. 2019;78:13-16

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. Enéas 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.[1] Nevertheless, the rate of any cardiac stent procedure declined by 27% between 2006 and 2009 after rising by 61% from 1999 to 2006.[1]

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.[2] 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.[3] 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).[4]

Heart Metab. 2019;78:13-16

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.[5] 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.[6] 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,[7] 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%).[8] 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.[9] 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

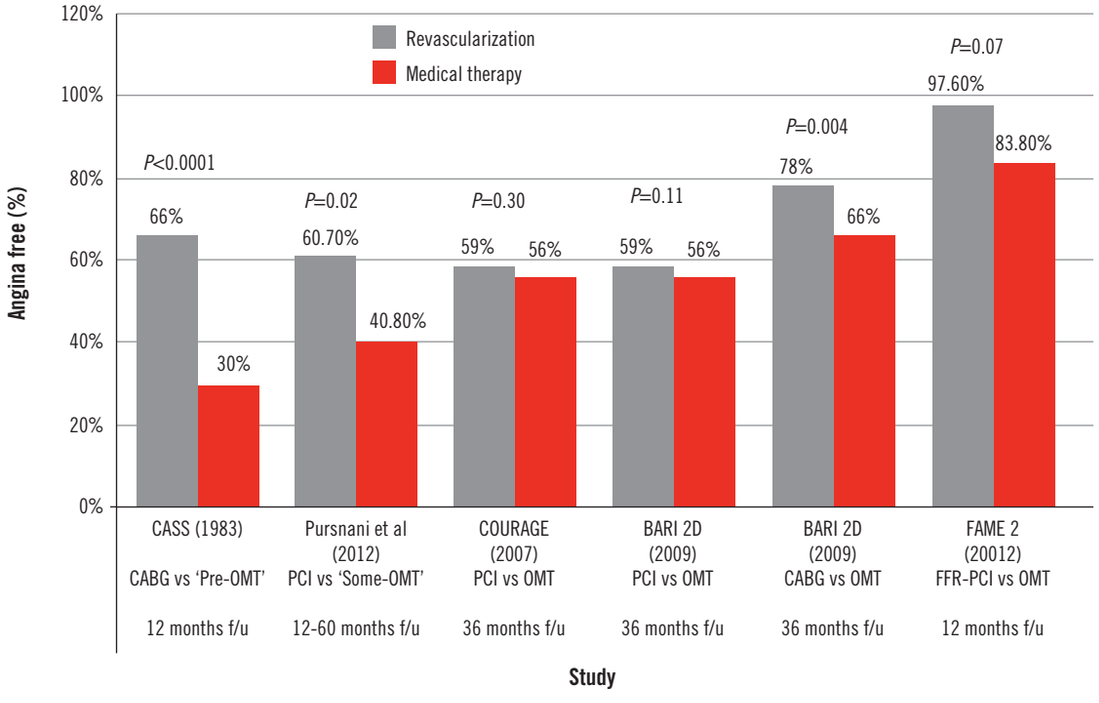

Fig. 1 *Rates of patients free of angina in selected clinical trials performed in the last 35 years comparing revascularization with medical therapy.*[5]

in combination.[10] 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[11]; 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.[12]

Structural	Functional
Residual disease or disease progression	Epicardial coronary spasm
In-stent restenosis/in-stent thrombosis	Microvascular dysfunction
Diffuse atherosclerosis	
Intramyocardial bridge	
Coronary dissection	

Table I *Main mechanisms implicated in recurrence/persistence of angina post-PCI.*

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.[13]

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%.[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.[14] More than a laboratory abnormality, several studies have demonstrated that periprocedural MI is associated with an increased risk of morbidity and mortality.[15-18]

It is believed that CI-AKI may occur in more than one third of patients undergoing coronary angiography or PCI,[19] 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[20] 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.[21] 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,[21] 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.[21]

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.[22] If we consider CAD not as a single clinical entity but rather as a syndrome with a multifactorial origin and different underlying physiopathological mechanisms, we may then appreciate post-PCI angina as a failure either to recognize that coronary stenosis was not the cause of angina

Heart Metab. 2019;78:13-16

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

1. Benjamin EJ, Muntner P, Alonso A, et al. Heart Disease and Stroke Statistics-2019 Update: A report From the American Heart Association. *Circulation*. 2019:CIR0000000000000659.
2. Huynh T, Perron S, O'Loughlin J, et al. Comparison of primary percutaneous coronary intervention and fibrinolytic therapy in ST-segment-elevation myocardial infarction: bayesian hierarchical meta-analyses of randomized controlled trials and observational studies. *Circulation*. 2009;119:3101-3109.
3. Peiyuan H, Jingang Y, Haiyan X, et al. The comparison of the outcomes between primary PCI, fibrinolysis, and no reperfusion in patients ≥ 75 years old with ST-segment elevation myocardial infarction: results from the Chinese Acute Myocardial Infarction (CAMI) Registry. *PLoS One*. 2016;11:e0165672.
4. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2018;39:119-177.
5. Patel AV, Bangalore S. Challenges with evidence-based management of stable ischemic heart disease. *Curr Cardiol Rep*. 2017;19:11.
6. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J*. 2019;40:87-165.
7. Borden WB, Spertus JA, Mushlin AI, Roe MT, McCoy LA, Redberg RF. Antianginal therapy before percutaneous coronary intervention. *Circ Cardiovasc Interv*. 2013;6:436-443.
8. Chan PS, Patel MR, Klein LW, et al. Appropriateness of percutaneous coronary intervention. *JAMA*. 2011;306:53-61.
9. Marzilli M, Merz CN, Boden WE, et al. Obstructive coronary atherosclerosis and ischemic heart disease: an elusive link! *J Am Coll Cardiol*. 2012;60:951-956.
10. Crea F, Camici PG, Bairey Merz CN. Coronary microvascular dysfunction: an update. *Eur Heart J*. 2014;35:1101-1111.
11. Gaglia MA, Torguson R, Lipinski MJ, et al. Frequency of angina pectoris after percutaneous coronary intervention and the effect of metallic stent type. *Am J Cardiol*. 2016;117:526531.
12. Crea F, Bairey Merz CN, Beltrame JF, et al. Mechanisms and diagnostic evaluation of persistent or recurrent angina following percutaneous coronary revascularization. *Eur Heart J*. DOI: 10.1093/eurheartj/ehy857. [Epub ahead of print]
13. Khan SU, Singh M, Lone AN, et al. Meta-analysis of long-term outcomes of percutaneous coronary intervention versus medical therapy in stable coronary artery disease. *Eur J Prev Cardiol*. 2019;26:433-436.
14. Lee DW, Cavender MA. Periprocedural myocardial infarction in contemporary practice. *Interv Cardiol Clin*. 2019;8:209-223.
15. Andron M, Stables RH, Egred M, et al. Impact of periprocedural creatine kinase-MB isoenzyme release on long-term mortality in contemporary percutaneous coronary intervention. *J Invasive Cardiol*. 2008;20:108-112.
16. Cavallini C, Savonitto S, Violini R, et al. Impact of the elevation of biochemical markers of myocardial damage on long-term mortality after percutaneous coronary intervention: results of the CK-MB and PCI study. *Eur Heart J*. 2005;26:1494-1498.
17. Jang JS, Hong MK, Park DW, et al. Impact of periprocedural myonecrosis on clinical events after implantation of drug-eluting stents. *Int J Cardiol*. 2008;129:368-372.
18. Feldman DN, Kim L, Rene AG, Minutello RM, Bergman G, Wong SC. Prognostic value of cardiac troponin-I or troponin-T elevation following nonemergent percutaneous coronary intervention: a meta-analysis. *Catheter Cardiovasc Interv*. 2011;77:1020-1030.
19. Rihal CS, Textor SC, Grill DE, et al. Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. *Circulation*. 2002;105:2259-2264.
20. Andreis A, Budano C, Levis M, et al. Contrast-induced kidney injury: how does it affect long-term cardiac mortality? *J Cardiovasc Med*. 2017;18:908-915.
21. Ben-Yehuda O, Kazi DS, Bonafede M, et al. Angina and associated healthcare costs following percutaneous coronary intervention: A real-world analysis from a multi-payer database. *Catheter Cardiovasc Interv*. 2016;88:1017-1024.
22. Goff SL, Mazor KM, Ting HH, Kleppel R, Rothberg MB. How cardiologists present the benefits of percutaneous coronary interventions to patients with stable angina: a qualitative analysis. *JAMA Intern Med*. 2014;174:1614-1621.