

Clinical update

Towards evidence-based percutaneous coronary intervention

The René Laënnec lecture in clinical cardiology[†]

Patrick A. Calvert^{1,2} and P. Gabriel Steg^{1,3,4*}

¹Hôpital Bichat, Assistance Publique-Hôpitaux de Paris, Paris, France; ²University of Cambridge, Cambridge, UK; ³INSERM U-698, Recherche Clinique en Athéromatose, Paris, France; and ⁴Université Paris Diderot, Paris, France

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Percutaneous coronary intervention (PCI) has matured from a pioneering adventure focused on feasibility to a major sub-specialty delivering real clinical results to patients. Despite delivering reductions in mortality and morbidity in the field of acute coronary syndrome and overcoming in-stent restenosis, several challenges still remain. Firstly, we need to adhere to practices supported by established trials: data relating to PCI in stable angina and late reopening of occluded infarct-related vessels suggest that this is not always the case. Secondly, we must develop new trials asking clinically relevant questions in 'real-world' populations that are focused on patient-based outcomes. Finally, given the current global financial crisis, it is now more important than ever that we demonstrate cost-effectiveness in our clinical practice. In these turbulent times, we discuss the challenges ahead for PCI in its journey towards evidence-based practice.

Keywords

Percutaneous coronary intervention • Myocardial infarction • Stable angina • Evidence • Cost-effectiveness

Introduction

Percutaneous coronary intervention (PCI) could represent the perfect paradigm of medical technology and innovation triumphing over adversity to deliver minimally invasive treatments to patients who previously received surgery or conservative management. Indeed, PCI has matured from the heady days of Andreas Gruntzig where the emphasis was on feasibility not efficacy. In the past 30 years, there have been major improvements in survival from coronary artery disease, in which PCI has played a real role, especially in acute coronary syndrome (ACS). However, significant challenges remain, not least of all the appropriate application of PCI, particularly given current global economic constraints. We discuss the successes of PCI and the challenges that remain if it is to fulfil its full potential.

Acute coronary syndrome: the triumph of percutaneous coronary intervention

There has been a major reduction in mortality in the general population as a result of improved survival from coronary heart disease.¹ Between 1970 and 2000, life expectancy in the United States increased by 6 years, with 3.9 years of the increase due to improved survival from cardiovascular disease¹ (Figure 1). Recent analyses show a continued reduction in deaths from coronary heart disease, with curative treatment (as opposed to risk factor modification) accounting for half of this reduction.² PCI has played a large part in these reductions in mortality, especially in ACS. French myocardial infarction registries show a reduction in

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* Corresponding author. Département de Cardiologie, Hôpital Bichat, 46 Rue Henri-Huchard, 75877 Paris Cedex 18, France. Tel: +33 140256601, Fax: +33 140258305, Email: gabriel.steg@bch.aphp.fr

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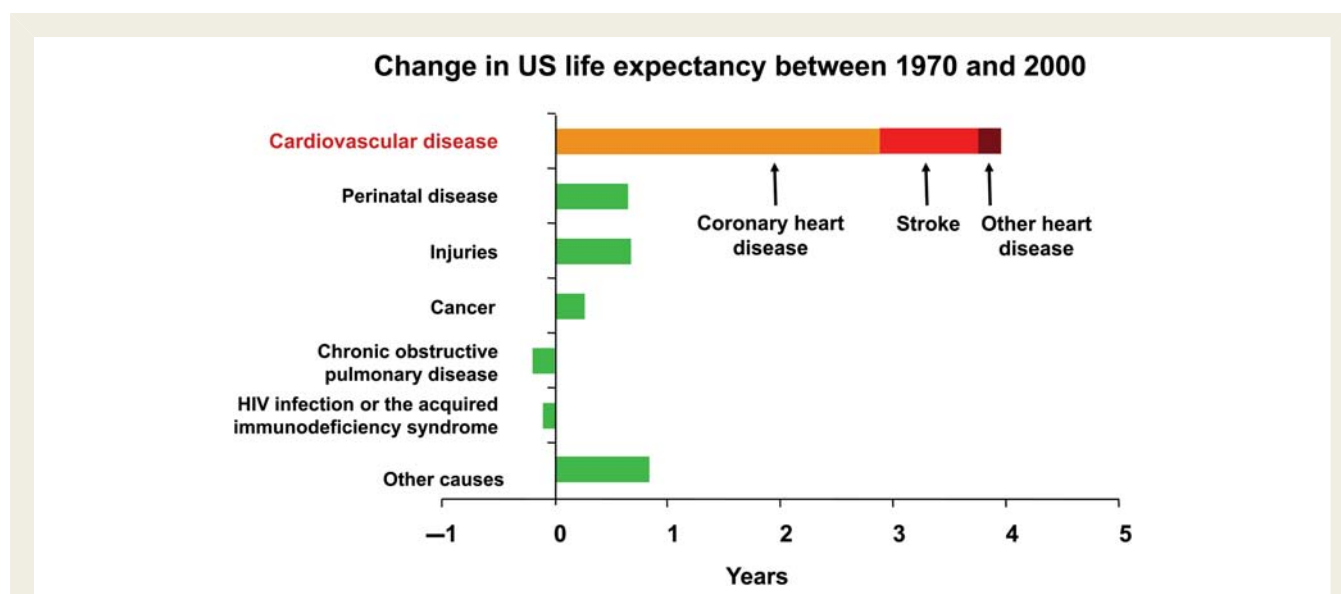


Figure 1 Change in life expectancy in the USA from 1970 to 2000. Adapted from Lenfant et al.¹

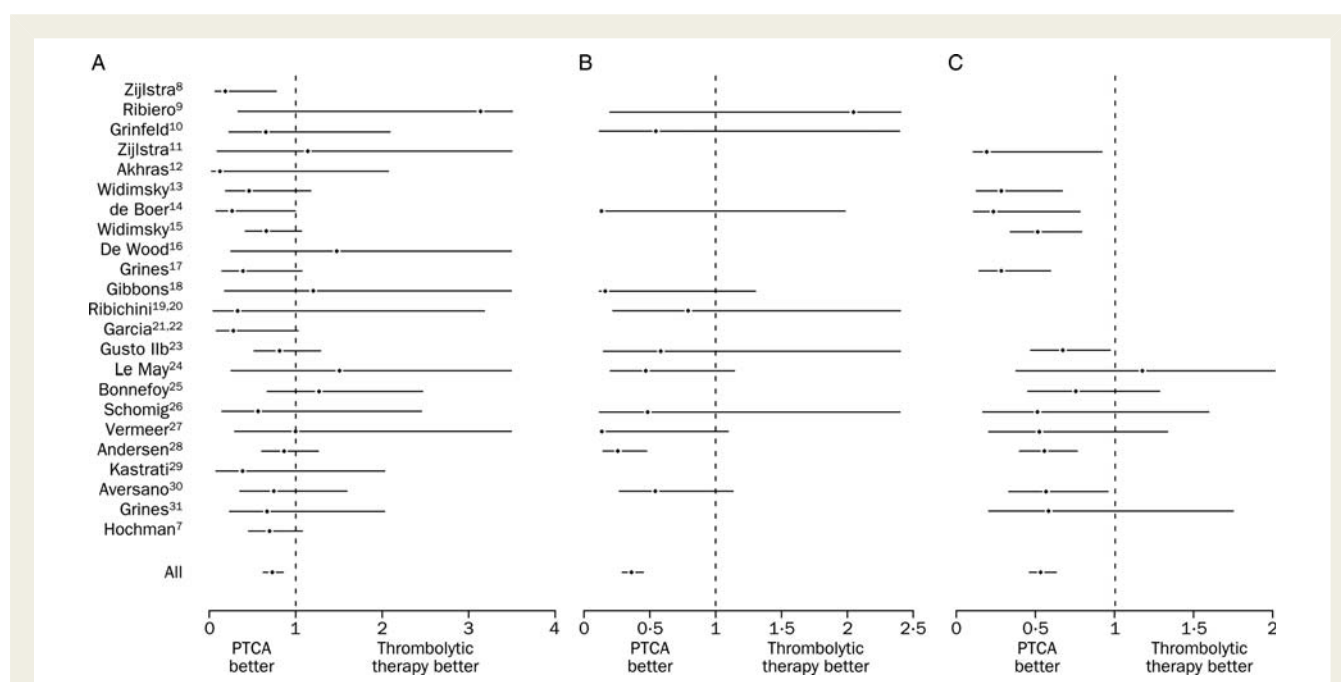


Figure 2 Systematic review of randomized trials of primary percutaneous coronary intervention vs. thrombolysis for ST-segment elevation myocardial infarction. Figure reproduced with permission from the publisher of Keeley et al.⁵ (the part labels of this figure and the reference numbers within the vertical axis relate to the original Keeley et al. article).

mortality with time while the uptake of primary PCI (PPCI) has increased.³ Likewise, the continuous national Swedish STEMI registry ($n = 61\,238$) between 1996 and 2007 showed a substantial and sustained reduction in mortality in parallel with increase in the use of evidenced-based therapies for STEMI, including PPCI.⁴ These associations should not be surprising given the firm evidence supporting PCI in STEMI, which is best summarized by the systematic review by Keeley et al.⁵ reporting on 23 randomized trials

comparing fibrinolysis with PPCI in STEMI and showing that the latter provided superior survival and clinical outcomes (Figure 2). In STEMI, patients treated with fibrinolysis, subsequent PCI is also beneficial, with several randomized trials demonstrating improved 30 days^{6,7} and 1 year⁸ outcomes compared with conservative management. In fact, the CAPTIM trial suggests that very early pre-hospital thrombolysis (i.e. within the first 2 h of symptom onset), when followed by early transfer to an

interventional centre, with broad access to PCI may improve survival compared with primary PCI^{9,10} and large European registry data have found consistent results.^{11,12} This is actually being tested by a prospective randomized trial, the strategic reperfusion early after myocardial infarction trial¹³ which will use early thrombolysis, optimized antithrombotic regimens with regimented access to subsequent PCI. Among the reasons that make such a strategy viable is the fact that there is often delay in the application of primary PCI^{14–16} and that this is clearly associated with suboptimal outcomes,^{17,18} making very early thrombolysis attractive when the PCI-related delay is expected to be too long.^{19,20} One possible solution to the issue of delayed implementation of primary PCI in STEMI may be the organization of regional networks of care able to provide timely primary PCI, which have been implemented in Europe¹² but also in the USA.²¹ Among patients with non-ST segment elevation-acute coronary syndromes, an early invasive strategy improves clinical outcomes in multiple trials, with a reduction in death or myocardial infarction (MI)²² although most of this benefit is derived from those patients in higher risk groups.²³ Therefore, PCI has contributed extensively to the improvement in outcomes in ACS patients, including improved survival.

Restenosis vanquished

Another major milestone in PCI was the development of stents and subsequently of drug-eluting stents (DES). Before stents became widely available, PCI produced haphazard acute results with often-unpredictable dissections leading to thrombosis, need for emergency surgery and high-death and MI rates. The advent of stents has allowed PCI to produce a consistent, predictable, and stable acute result, but did not address the remaining complication of in-stent restenosis. After decades of unsuccessful attempts to prevent restenosis using systemic drug therapy, including dozens of failed randomized trials, local drug delivery using DES successfully addressed this problem. The landmark RAVEL trial showed the ability of the first-generation DES to reduce and nearly abolish restenosis.²⁴ Subsequently, concerns were raised regarding the long-term safety of these devices,²⁵ particularly the risk of early, late, and very late stent thrombosis and the need for protracted antiplatelet therapy, with its attendant risks, costs, and inconvenience. However, continued improvement in DES technology, in terms of drugs, polymers, and delivery platforms, has resulted in newer generations of DES which achieve nearly 'perfect' clinical results, with clinically insignificant rates of restenosis and stent thrombosis, e.g. in a large recent multi-centre trial using the latest generation of everolimus-eluting stents, the 12-month ischaemia-driven target lesion revascularization rate was 2.3% and the 12-month stent thrombosis rate was 0.29%.²⁶ Thus, restenosis, the proverbial 'Achilles heel' of PCI, has been vanquished, a truly phenomenal achievement. There remain however some residual challenges for DES: while the risks of acute and subacute stent thrombosis appear nowadays similar and even lower with new DES than with bare metal stents, there remain uncertainties regarding the risks of very late stent thrombosis, which may continue to accrue over time beyond the first years after stent implantation.²⁷ Even though these risks appear low, the complications

associated with these events are severe.²⁸ Bioabsorbable stents may be the solution to this remaining hurdle.²⁹

Another interesting feature of PCI is the ability to provide myocardial revascularization in patients who are too sick or too frail to undergo coronary artery bypass grafting. This may be related to advanced heart failure, advanced comorbidities (due for example to renal or liver or respiratory failure), very poor functional status or advanced age and frailty, in a manner very similar to what is seen in elderly patients with aortic stenosis who may be too sick to undergo surgical valve replacement. In such 'last resort' patients, PCI often provides a short-term solution for revascularization in patients with severe or intractable symptoms, even if it is not always as complete and as durable as that which would be provided by surgery, with an often modest procedural risk, cost, and length of stay. While there are few studies devoted to this heterogeneous group of patients, PCI clearly provides an additional option to the management of high-risk patients with severe myocardial ischaemia.

Things are not always as they seem

Yet, despite its resounding successes, PCI is not a therapy warranted for every patient with coronary artery disease. In fact, there are large groups of patients in whom it has no proven benefit, even when theoretical considerations might have suggested otherwise.

Among MI patients with a persistent occlusion of the infarct-related artery (regardless of whether it is related to lack of provision of reperfusion therapy or to an unsuccessful fibrinolysis), there is a theoretical advantage in recanalizing the occluded vessel. It may improve left ventricular function as well as electrical stability, and provide a potential collateral channel in case of subsequent occlusion of contralateral arteries. Several observational studies had appeared to support the concept that routine recanalization of the occluded infarct artery using PCI would be associated with clinical benefit (the 'late open artery hypothesis').³⁰ Yet, clinical trials have failed to support the late reopening of occluded infarct-related vessels in patients without post-infarct angina or shock. The large international occluded artery trial (OAT) showed a non-significant trend towards harm for PCI in these patients³¹ with a combined primary endpoint of death, MI or NYHA IV heart failure of 17.2% in the PCI group and 15.6% in the medical group at 4 years ($P = 0.20$). Subgroup analyses according to ejection fraction, timing of presentation,³² collateral circulation,³³ viability,³⁴ and vessel-treated³⁵ as well as longer term follow-up results³⁶ are all consistent with the original report. These results were confirmed in a meta-analysis of available randomized-controlled trials examining this issue.³⁷ Accordingly, PCI of a totally occluded infarct-related artery >24 h after acute MI is not recommended in asymptomatic patients, (class IIIB recommendation in the European Society of Cardiology STEMI guidelines).³⁸

A large group of candidates for PCI are patients with stable coronary artery disease. Again, there is an apparent logical—theoretical justification for the routine use of PCI in that population: once a severe coronary artery stenosis is identified, treating it with a coronary stent might appear a logical strategy to prevent stenosis

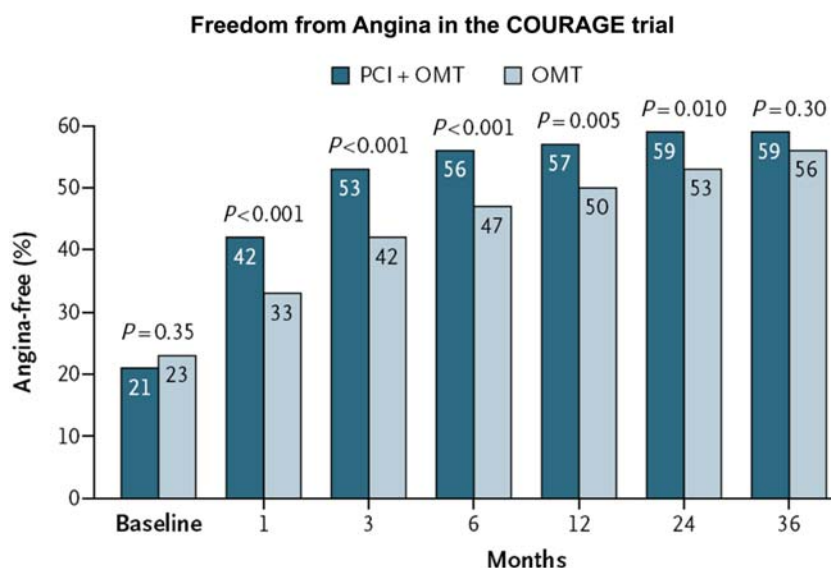


Figure 3 Freedom from angina, as measured by the Seattle Angina Questionnaire frequency score in the COURAGE trial. Adapted from Weintraub et al.⁴³

progression or instability leading to ACS and death. However, current data suggest that there is no mortality benefit for PCI in patients with stable angina. A meta-analysis by Katritsis and Ioannidis³⁹ examined the results of 11 trials and found no difference between PCI vs. conservative medical management of stable angina for death and cardiac death or MI. Another meta-analysis of 61 RCTs showed similar results.⁴⁰ The COURAGE trial randomized 2287 patients with stable angina to PCI plus optimal medical therapy (OMT) or OMT alone.^{41,42} After 7 years of follow-up, the primary endpoint of death and MI occurred in 19.0% and 18.5%, respectively (HR = 1.05, $P = 0.62$). Although PCI was slightly more effective than OMT alone at treating angina, its advantage was modest and not long lasting with 59% vs. 56% ($P = 0.30$) of patients free from angina at 3 years⁴³ (Figure 3), leading to the conclusion that PCI results in small incremental benefits in health status compared with OMT, which disappeared by 36 months. Several,^{44,45} but not all,⁴⁶ meta-analyses have confirmed that there are no benefits of routine PCI on major adverse clinical events and that the impact of PCI on anginal symptoms is at best modest. Overall, routine PCI of stable patients with coronary artery disease (CAD) is not a good clinical option and is not cost-effective.⁴⁷ These results have been interpreted diversely: some have argued that this was to be expected as PCI is mostly effective at relieving symptoms. Others have questioned the design, conduct, and interpretation of COURAGE.^{48–50} Another group of potential candidates for PCI are diabetic patients with CAD: it is well established that diabetic patients die primarily of cardiovascular disease, with coronary artery disease playing a major role. Because diabetic patients often have few or no anginal symptoms, a policy of routine screening for coronary artery disease with revascularization would seem like a good idea in order to try to reduce mortality in this high-risk patient group. Yet, the

large BARI-2D trial found no improved survival free from death, MI or stroke in diabetic patients with stable coronary artery disease randomized to revascularization when compared with OMT alone (77.2% vs. 75.9%, $P = 0.70$) at 5 year follow-up.⁵¹ Stratification of the cohort according to type of revascularization showed a lower rate of the combined endpoint when revascularization was coronary artery bypass surgery (22.4% vs. 30.5%, $P = 0.01$) but not when revascularization was PCI (23% vs. 21.1%, $P = 0.15$).

Failure of percutaneous coronary intervention to improve clinical outcomes in patients with stable coronary artery disease: a matter of the wrong target?

Why should patients with stable coronary artery disease fail to accrue prognostic benefit from PCI? This may, at least in part, be related to the fact that the highest risk patients (who arguably stand to benefit the most from revascularization) are often excluded from these trials. Patients with 'a markedly positive stress test' were excluded from the COURAGE trial, whereas patients with left main stem lesions were excluded from the BARI-2D study. Yet, patients from both of these trials were not at particularly low risk, so selection of low risk patients cannot account for the failure of routine PCI in these trials to improve outcomes. 'Significant' coronary artery stenosis, as defined by coronary angiography, was a major inclusion criterion of all of these trials. Coronary angiography is a poor assessor of the extent and severity of actual coronary artery disease when compared with

autopsy or intravascular ultrasound.⁵² In addition, there is only a weak correlation between angiographically determined coronary stenosis severity and functional significance.⁵³ We also know that the majority of coronary plaques responsible for acute MI are non-flow limiting with 132 out of 194 culprit plaques having a stenosis less than 50% in one series.⁵⁴ However, a natural history study of plaque progression suggested that a minimal luminal area less than 4 mm² was one of three factors independently associated with future adverse events.⁵⁵ Nonetheless, PCI in stable angina patients may not confer prognostic benefit because we may not be stenting the right lesions. It would appear more logical and potentially beneficial to focus on lesions that are either responsible for large areas of ischaemia or are likely to result in MI. The former can be assessed by either non-invasive imaging or measurement of fractional flow reserve (FFR) (because FFR is related both to the degree of stenosis as well as to the size of myocardium at risk). However, identifying which plaques are likely to result in MI is more challenging. Natural history studies using virtual histology intravascular ultrasound (VH-IVUS) to identify thin-capped fibroatheroma (TCFA) suggest that they are associated with increased MACE rates compared with other plaques (HR = 3.35, $P < 0.001$)⁵⁵ and (HR = 7.53, $P = 0.036$).⁵⁶ However, the limited axial resolution of VH-IVUS of 150 µm⁵⁷ is insufficient to identify the 65 µm limit of the histology-identified TCFA that is responsible for 70% of thrombotic vessel occlusion in sudden cardiac death.⁵⁸ Thus, VH-IVUS overestimates the number of TCFA and hence it is unlikely that prophylactically stenting these lesions will reduce MACE. Although optical coherence tomography does have sufficient resolution (15 µm), no natural history studies are, as yet, forthcoming. Therefore, PCI is an effective (and relatively safe) treatment for potentially dangerous coronary artery plaques but we do not yet know how to reliably identify these.

The way forward

As PCI matures from adolescence to adulthood, what must we do in order to ease this painful transition? Firstly, we must concentrate on clinically valid outcomes. The early development of PCI has been dominated by technological evolution. Although impressive, it has fostered a culture of device- and lesion-related outcomes. We need to move away from technical feasibility and focus instead on clinical efficacy, regardless of the technological sophistication. Hence, therapeutic efficacy must be measured in hard clinical outcomes particularly cardiovascular death, MI and stroke. An additional 'twist' to this issue is the need to ensure quality, documenting precisely the safety and efficacy of our interventions. For instance, PCI often results in periprocedural myocardial necrosis. This has often been 'swept under the rug' and labelled as 'troponin leaks', perceived to have little or no impact on subsequent clinical outcomes. There is some controversy as to what is the exact clinical impact of periprocedural MIs, with some studies suggesting that these have no impact on long-term mortality,⁵⁹ whereas others found that all types of MI increase mortality.⁶⁰ Regardless of the magnitude of the risk, capturing information regarding procedural complications, including periprocedural infarctions, is an important and legitimate quality insurance process. Procedural quality is also related to expertise and volume

of both the operator and the centre. While it is difficult to precisely document the impact of a lower volume or the threshold at which volume impacts outcomes for elective procedures, there is documentation in the setting of ACS that lower volume, non-specialized primary PCI centres achieve longer delays to primary PCI, lower use of evidence-based therapies and possibly higher mortality.^{15,61,62}

Secondly, we must expand our evidence base with trials that are both clinically valid and generalizable to the target population. Such external validity of clinical trials is one key facet of future clinical trial design: minimizing selection bias requires a broad enrolment base of representative patient groups, restriction of exclusion criteria, participation of a large number of enrolling sites, representative of routine clinical practice, and the use of simple designs. These strategies enable enrolment of substantial proportions of the target population. The ongoing Swedish thrombus aspiration in ST-elevation in Scandinavia trial demonstrates that this is feasible: this trial aims to test the value of thrombus aspiration as an adjunct to primary PCI.⁶³ Currently, with several thousand patients already in the trial, participating centres in Sweden are able to enrol more than two-thirds of all PPCI patients in the entire country, and the proportion of enrollees at each Swedish PCI centre ranges from 30% to 86% of all PPCI patients (S.K. James, personal communication). The ultimate strategy for ensuring external validity is the 'all-comer' approach, in which centres approach 100% of potential trial candidates for enrolment. This approach has been used successfully in several recent PCI trials,^{64–66} although even in some of these trials, up to half of screened patients were ultimately excluded from randomization. Another important feature of modern trials is the ability to enrol and follow-up effectively and at a low cost, large patient numbers and, as often as possible, to do this independently of industry. In that respect, the experience of the Danish SORT OUT trials,^{67–69} relying on a non-profit, industry-independent academic collaboration in which patients are enrolled using an all-comer approach and follow-up is collected through existing national registries, shows that this is feasible and effective, circumventing many of the problems faced by modern cardiovascular clinical trials.⁷⁰ Expanding the evidence base will rely on key international trials such as the upcoming International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial (www.clinicaltrials.gov identifier NCT01471522) which will enrol stable patients with moderate to severe myocardial ischaemia and randomizes them to a strategy of OMT with cardiac catheterization and optimal revascularization or a conservative strategy of OMT with catheterization reserved for patients with refractory angina, ACS, acute heart failure, or cardiac arrest. This trial will be key in establishing the role of coronary angiography and revascularization in patients with stable coronary artery disease (www.ischemiatrial.org).

Thirdly, we need to apply and use the available evidence. The OAT shows that there is no benefit in reopening late presenting infarct-related vessels in the absence of ongoing symptoms or shock,³¹ and these findings are supported by a meta-analysis³⁷ and recommended in guidelines.³⁸ However, data from the CathPCI registry including 28 780 patient visits in 896 hospitals in the United States suggest that neither the publication of OAT,

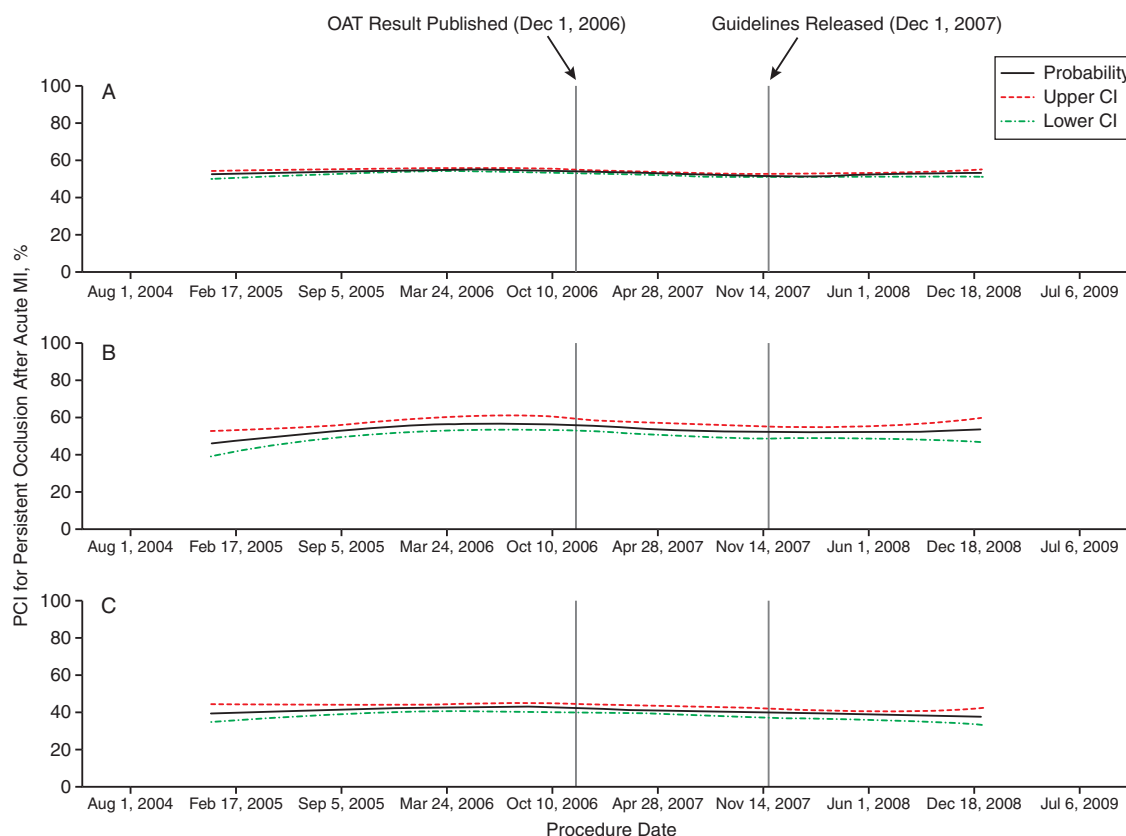


Figure 4 Impact of Guideline Recommendations for Revascularization of Persistently Occluded Infarct-Related Arteries in the USA. Unadjusted rates of percutaneous coronary intervention for occlusions identified after myocardial infarction over time. (A) Overall (B) for STEMI (C) restricted to hospital with most diagnostic catheterization procedures. Data from the Cath percutaneous coronary intervention registry 2005–8. Adapted from Deyell *et al.*⁷¹

nor the publication of guidelines has altered the rate of PCI in 'OAT-like' patients⁷¹ (Figure 4). Similarly, the COURAGE trial showed no incremental advantage of PCI on outcomes other than angina-related quality of life in stable angina, suggesting that a trial of OMT is warranted before PCI.⁴¹ However, data from the US National Cardiovascular Data Registry (NCDR) including 467 211 patients suggest that there was a low uptake of OMT (use of or documented contra-indications to anti-platelet, beta-blocker, and statin) both before and after publication of the COURAGE trial (43.5% vs. 44.7%, $P < 0.001$).⁷² This translates into worrying data from the NCDR registry ($n = 144\,357$) which suggests that 38% of non-acute PCI is of 'uncertain' appropriateness according the ACCF/SCAI/STS/AATS/AHA/ASNC appropriateness criteria for coronary revascularization,⁷³ whereas 11.6% are inappropriate⁷⁴ (Figure 5). Clearly, we need to improve our adherence to evidence-based guidelines. More generally, the era of unreviewed decision-making for revascularization is over and indications for interventions, particularly in the elective setting, are best decided by a heart team involving the patient's cardiologist, the interventionalist, and the surgeon, which should offer the patient an informed decision-making process.

Fourthly, in order to use interventions in the most rational way, it is crucial to be able to assess the patient risk and anatomic complexity. A host of clinical, functional, and angiographic scores are being developed to do so, which hopefully will assist in targeting patients most likely to derive benefit from PCI. Good examples of such scores are the EuroSCORE,⁷⁵ the STS score,⁷⁶ and the SYNTAX score.⁷⁷ It was established, for instance, that the SYNTAX score was useful in selecting PCI or CABG for revascularization among patients with severe multi-vessel disease, with patients having a high score deriving greater clinical benefit from CABG than from PCI, whereas this was not seen at moderate or low SYNTAX scores.⁷⁷ Future scores will hopefully help us better profile our patients and improve management decisions.

Finally, with mounting economic challenges, it is our responsibility to demonstrate that our investigations and treatments, including PCI, provide value as well as clinical efficacy. The concept of rationing healthcare according to cost is always uncomfortable for both physicians and patients. However, providing cost-effective therapies is not a new concept and we would be well advised to provide such evidence supporting our practices before governments and health insurance providers make decisions in our

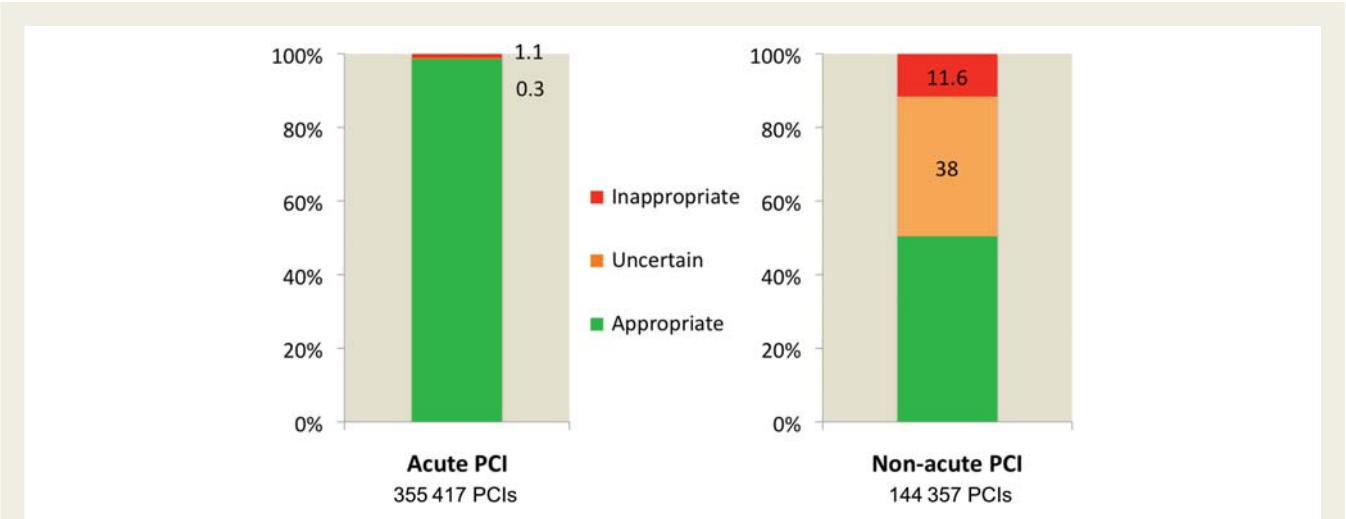


Figure 5 Appropriateness of percutaneous coronary intervention in the USA in the National Cardiovascular Data Registry 2009–10, according to the ACCF/SCAI/STS/AATS/AHA/ASNC 2009 appropriateness criteria for coronary revascularization. Adapted from data from Chan et al.⁷⁴

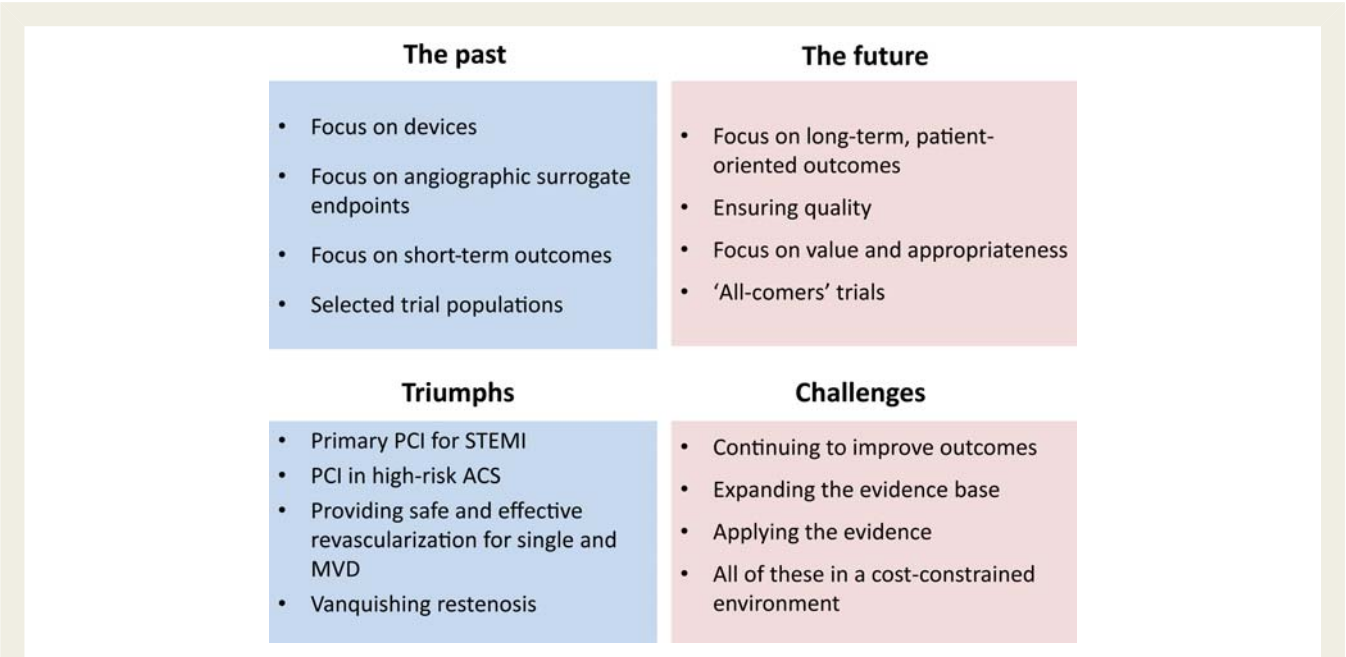


Figure 6 Successes and challenges of percutaneous coronary intervention.

place. For example, existing data suggest that liberal (in fact, nearly systematic) vs. slightly more selective use of DES (in 92% vs. in 68% of patients) provides no real advantage when compared with several benchmarks for cost-effectiveness.⁷⁸ Beyond the mere selection of DES vs. BMS, the number of stents placed in a given patient and how these costs relate to those of surgical revascularization are important topics. Other data suggest that revascularization is only associated with a lower risk of cardiac death in those

with greater than 10% ischaemia.⁷⁹ Routine use of revascularization in patients with no or minimal ischaemia is unlikely to provide clinical benefit in terms of hard outcomes. Hence, a threshold of ischaemia could be proposed as a trigger for PCI in stable angina patients and indeed the ISCHEMIA trial is only enrolling patients with at least moderate ischaemia.

In conclusion, in its short lifetime, PCI has changed from a pioneering adventure dominated by exciting technological

advancements but rather light on long-term, patient-oriented outcomes to a mature sub-speciality supported by a robust evidence base (Figure 6). However, despite these triumphs, many challenges remain. If PCI is to truly fulfil its potential, these challenges must be met with the same enthusiasm and rigour that saw the birth of PCI, 34 years ago.

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