Why we need a national registry in interventional cardiology

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ABSTRACT

- Percutaneous coronary intervention (PCI) is increasingly used in the management of acute coronary syndromes and refractory angina, and technical advances such as drug-eluting stents (DES) and potent antithrombotic therapies (such as clopidogrel and glycoprotein IIb/IIIa inhibitors) have been heralded as improving long-term outcomes.
- Offsetting these advances has been: considerable concern about the safety of DES in regard to late stent thrombosis and antithrombotic drug-induced bleeding; the rising use of PCI and DES in clinical situations where evidence of efficacy is lacking; preferential use of PCI in low-risk populations; and limited cost-effectiveness data comparing PCI with other treatments.
- There are few contemporary data in Australia on the efficacy, safety and costs of PCI — as used in everyday clinical practice — that matches clinical outcomes with baseline patient characteristics, indications for intervention, coronary anatomy, procedural technique, co-interventions and site of care.
- A national registry that prospectively collects standardised data on processes and outcomes of PCI is warranted. This would ensure safe and appropriate evidence-based use of limited resources in an era of expanding use of PCI in clinical circumstances not tested in randomised trials.

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Percutaneous coronary intervention (PCI), comprising coronary angiography and angioplasty, has burgeoned as a less invasive means of revascularising coronary arteries than coronary artery bypass grafting (CABG). Stent insertion to maintain patency of the dilated artery and the substitution of drug-eluting stents (DES) for bare-metal stents (BMS) have been used to lower rates of restenosis. PCI has lessened the demand for CABG, and more patients with acute coronary syndromes (ACS) or limiting angina, who would not previously have been considered candidates for coronary revascularisation, are now undergoing PCI. In Australia, about 30 000 PCIs with stenting are performed each year, and the numbers continue to grow.[1]

However, it remains uncertain as to whether current PCI use reflects evidence-based medicine in maximising population health and return on investment. Resolving this issue in Australia may require the establishment of a national registry of PCI procedures.

How effective and safe is PCI in clinical trials?

Acute coronary syndromes

Systematic reviews of randomised trials have shown primary PCI, if performed expeditiously, to be superior to fibrinolytic therapy in patients presenting with evolving ST-elevation myocardial infarction (STEMI) in reducing the relative risk of death by 32% and of re-infarction by 52% at 6 months.[2] Benefit is also seen in patients with STEMI complicated by cardiogenic shock[3] and where PCI is used to rescue failed thrombolysis.[4] However, the superiority of PCI rests on door-to-balloon times being less than 90 minutes;[5] opening the occluded artery with PCI some days after a STEMI in stable patients with no recurrent ischaemia has no effect on outcomes.[6]

In patients with non-ST-elevation ACS (NSTEACS), early (within 48 hours) PCI in all or most patients ("routine invasive" approach) compared with PCI in only those 30%–45% of patients with spontaneous or inducible ischaemia after initial aggressive medical therapy (selective "conservative" approach) resulted in 25% less re-infarction and recurrent angina up to 5 years after PCI.[7] However, this benefit was achieved with an increased risk of early inhospital mortality and bleeding, with no overall change in all-cause mortality.

Stable coronary disease

Previous systematic reviews[8] and more recent trials[9] have not shown PCI to be superior to optimal medical therapy in reducing risk of death or ACS in patients with stable coronary disease, although this may reflect underpowered trials. While PCI is initially more effective than medical therapy in relieving angina, this effect diminishes with time. A recent meta-analysis demonstrated CABG to be more effective than PCI in relieving angina, with fewer repeat revascularisations and similar 10-year survival.[10] These comparative benefits of CABG are even more pronounced and are associated with a survival benefit in patients with multivessel coronary disease.[11]

Drug-eluting stents versus bare-metal stents

The relative efficacy and safety of DES compared with BMS have been subject to much debate, with Australian[1] and United States[12] experts recently urging caution in DES use. Trials published during the 1990s had shown DES reducing restenosis rate (and need for repeat revascularisation) by up to 70% compared with BMS during the first 6 to 12 months.[13] However, these trials were of short duration (no more than 1 year); were underpowered to assess myocardial infarction (MI) and mortality; and did not assess for late stent thrombosis (LST), a consequence of DES-induced impaired endothelialisation of the culprit stenosis. Compared with early restenosis, LST is uncommon but carries a much higher risk of MI (70% v 10%), with mortality rates between 31% and 45%.[14]

In the BASKET-LATE (BAsel Stent Kosten Effektivitäts Trial – LAte Thrombotic Events) trial, DES patients showed higher rates of LST (1.4%) and thrombosis-related events (2.6%) than BMS patients who discontinued clopidogrel (0.8% and 1.3%, respectively).[15] Meta-analyses confirm a risk of LST (excess of 0.5%) at more than 12 months in DES patients compared with BMS patients,[16] with recent data suggesting this risk is confined to paclitaxel-eluting stents.[17] Observational studies suggest that premature cessation of dual antiplatelet therapy in patients with DES may act as the trigger, as mortality rates were lower among patients taking clopidogrel beyond 30 days and up to 24 months after PCI than among those discontinuing it (0.7% v 7.5%[18] and 2.0% v 5.3%,[19] respectively). Trials are needed to determine the optimal

duration of clopidogrel therapy following PCI, and to determine optimal anticoagulant strategies in circumstances where clopidogrel needs to be temporarily or permanently discontinued (such as imminent surgery).

On the positive side, a comprehensive analysis of 38 trials (18 023 patients) published to March 2007 indicates 58%–70% less restenosis-related target vessel revascularisation (TVR) with DES than with BMS. Also noted is a 17%–19% reduction in the relative risk of recurrent MI with sirolimus-eluting stents compared with paclitaxel-eluting stents or BMS.[17] However, there were no consistent reductions in mortality.

However, a critical appraisal of all randomised controlled trials and registry-based studies published to November 2005[20] concluded that the clinical benefits of DES were subject to overestimation owing to:

- inferior BMS comparators in most trials, which used older stents with thicker struts (130–140 μm thick) associated with higher restenosis risk than currently available thin stents (62–91 μm thick);
- protocol-mandated coronary angiography within the first 12 months, which biased the revascularisation rate against the BMS group because of visualisation of asymptomatic lesions that would not otherwise have attracted intervention;
- over-reliance on angiographic surrogates (such as late lumen loss) and clinician-mediated endpoints of TVR separate from death or MI risk;
- attenuation of restenosis benefit in high-risk cohorts; and
- underestimation of the risk of LST.

How cost-effective is PCI?

No three-way randomised comparisons of the cost-effectiveness of PCI, CABG and medical therapy have been reported to date. Cost-effectiveness studies comparing routine management with conservative invasive management for NSTEACS suggest that the former is cost-effective, at about US$12 739 per life-year gained,[21] but estimates are limited to the first 6 months after index hospitalisation and do not account for medium- to long-term events. In the case of stable coronary disease, CABG is definitely more cost-effective than medical therapy, which in turn is more cost-effective than PCI, even in "real-world" studies that have compared appropriate, guideline-concordant use of all three methods in unselected patients.[22] Choosing DES rather than BMS renders PCI even less cost-effective, with estimated Australian costs up to A$46 829 per quality-adjusted life year (QALY), close to the accepted cost-effectiveness threshold of around A$50 000.[23] Finally, cost-effectiveness estimates from different trials range widely, from US$25 540 per QALY gained (in the SIRIUS [Sirolimus-Eluting Balloon Expandable Stent in the Treatment of Patients with De Novo Native Coronary Artery Lesions] trial)[24] to as high as US$128 744 (in the BASKET trial).[25] Cost-effectiveness in most trials has probably been overestimated owing to underestimation of stent use rate per patient (as multi-lesion stenting becomes more prevalent), overestimation of the reduction of TVR by DES, and failure to measure downstream costs of late complications due to LST and bleeding induced by dual antiplatelet therapy.[18]

Use of PCI in the real world

Maximisation of clinical benefits and cost-effectiveness will be more likely if PCI is performed preferentially on patients with trial-validated indications and high baseline risk of death or future coronary events: those with early-phase STEMI, intermediate- to high-risk NSTEACS, or severe limiting angina due to multivessel disease refractory to optimal medical therapy and otherwise unsuitable for CABG.

However, US registry data indicate that about 85% of all PCI procedures are undertaken electively in patients with stable coronary disease.[26] In the minority of patients with STEMI undergoing primary PCI, this occurs within 90 minutes in fewer than 5% of patients transferred from non-PCI-capable facilities,[27] and in general PCI is used more frequently in low-risk than high-risk patients.[28] Surveys of invasive cardiologists in the US suggest a bias towards performing PCI in situations lacking evidence of benefit,[29] such as treating stable ischaemia,[8] opening infarct-related occluded arteries,[6] and intervening on multiple as opposed to single "culprit" lesions.[30] Any potential overuse of PCI is being matched with an underuse of effective medical therapy: no more than 50% of eligible patients with NSTEACS in the GRACE (Global Registry of Acute Coronary Events) registry received all indicated therapies.[31]

DES accounted for 85% of all stent insertions to 2006 in the US, at least half of which were performed for what were, at the time, "off-label" or untested indications in higher-risk patients, including those with diabetes.[32] Such patients had coronary lesions more prone to restenosis than those in pivotal trials: long lesions, chronic or small-vessel occlusions, calcified or bifurcation lesions, and vein-graft lesions. The benefits, if any, of using DES over BMS for off-label indications are only now being assessed in trials and registries which, to date, feature small numbers of patients, surrogate outcomes (such as late luminal loss and restenosis), results yet to be published in peer-reviewed journals, or no definitive differences in rates of major adverse cardiac events (MACE).[33] Data from three registries have shown higher rates of TVR at 12 months in off-label indications than in standard indications in patients receiving DES (7.6% v 4.4%,[34] 6.3% v 2.4%,[35] and 12.7% v 7.7%;[36] $P < 0.001$ for all comparisons), although the most recent report indicates significantly lower mortality with DES than with BMS for off-label indications (3.7% v 6.4%; $P < 0.001$).[36]

The registry literature comparing DES with BMS is littered with conflicting reports. For example, a large Swedish registry study reported an absolute increase in mortality of 1.5% at 3 years in DES patients,[37] but this was no longer seen at 4 years.[38] A Swiss study over 3 years also reported 1.5% excess mortality but with no apparent flattening of the cumulative stent thrombosis curve over time, suggesting ongoing risk.[39] Another observational study indicated that LST risk could be two- to threefold higher, up to 1.3% per year.[14] In contrast, a Canadian registry study to 2 years, in which patients received clopidogrel for 12 months after PCI, suggested no DES-related excess in stent thrombosis, MI or mortality compared with BMS,[40] and a US study of patients with both simple and complex lesions showed significant reductions in adjusted rates of TVR and MACE in favour of DES.[41] As of mid 2008, the cumulative observational evidence is increasingly reassuring that prevention of restenosis achieved by DES does not come at the expense of an increase in death or MI compared with BMS.[42,43]

Requirements and potential uses for a national percutaneous coronary intervention (PCI) registry

- Funding from government (state/territory and/or federal) with sponsorship from professional societies and public foundations (as exemplified by the Australia and New Zealand Dialysis and Transplant Registry and the Australian Orthopaedic Association National Joint Replacement Registry).
- Data repository at an independent academic site (eg, university, Australian Institute of Health and Welfare) that can undertake analyses involving risk adjustment and ascertainment of long-term outcomes (mortality, re-infarction, re-hospitalisation for coronary events and procedures, quality of life) using linked databases and population surveys.
- Universal participation by all PCI-capable institutions and invasive cardiologists, both public and private (a possible future requirement for institutional accreditation) linked with feasible but statistically representative sampling of patients undergoing PCI.
- Agreed-on data elements, outcome measures, methods of data collection and follow-up, and analytical techniques that are methodologically sound and subject to external quality auditing.
- Agreed-on analytical outputs that are used (by professional groups, consumers, health policymakers and researchers) for monitoring institutional and professional performance, identifying needs gaps in PCI services, guiding quality improvement initiatives and informing resource allocation.
- Appropriate governance structure to protect the privacy of consumers, professionals and institutions, and to minimise bias and political interference in the analysis and reporting of data. ◆

The disparity in results from trials and registry studies may relate to differences in study enrolment criteria (for both patients and coronary anatomy), definitions of stent thrombosis and other clinical events, clinical thresholds for repeating TVR, number of stents inserted, adequacy of stent placement, type and duration of post-PCI antiplatelet therapy, and follow-up period. The risk of PCI-related bleeding in routine practice also needs closer scrutiny with the advent of more potent antithrombotic agents, with registry data reporting a 5.5% incidence of major periprocedural bleeding associated with a 64% increased risk of inhospital death in patients undergoing PCI for ACS.[44] More data are needed on the risk of bleeding associated with long-term use of dual antiplatelet therapy — particularly in patients receiving warfarin prophylaxis for atrial fibrillation (in whom major bleeding rates as high as 7% per year have been reported)[45] — and the risk of re-infarction if such therapy needs to be discontinued at the time of surgery.

What is the current state of play in Australia?

Given the uncertainties around efficacy, safety and cost-effectiveness, what is the current state of play of PCI use in Australia in 2008? Frankly, we have few data from which to get a clear idea. According to the most recent statistics, the annual number of PCI procedures has more than doubled from 80 per 100 000 population in 1996–97 to 170 per 100 000 in 2005–06,[46] with significant variation in per-capita rates between states. DES use has increased exponentially, accounting for virtually all stents inserted in the private sector in 2006 and about 30% in the public sector.

However, the last detailed analysis of PCI in terms of indications, patency rates, survival and complications was published in May 2002, based on data collected within the Coronary Angioplasty Register between 1980 and 1999.[47] In that period, 42% of angioplasties were performed in patients with stable angina, 42% in patients with unstable angina, and 7% as either primary or rescue angioplasty for STEMI. Virtually all procedures (92%) reported in 1999 involved BMS (as DES were not yet available) and more than 85% targeted single vessel disease, among which 38% of lesions affected the left anterior descending artery. The vast majority (95%) of procedures were judged successful; the remainder involved complications requiring urgent CABG in fewer than 1% of cases, peri-procedural acute MI in 1.2%, other arterial complications such as stroke in 1.2%, and death in 0.8%. While these data appear reassuring, 10 of 57 hospitals (accounting for 15% of procedures) did not provide data, and those that did provided incomplete data for some variables.

In a more contemporary national cohort of 3402 patients presenting with ACS to 39 centres (29 PCI-capable), angiography was undertaken in 57% of patients, of whom half underwent PCI, and 57% of those received DES.[48] The timing of these procedures and long-term outcomes were not reported. This audit also showed that only 58% of patients with STEMI, 35% with non-STEMI and 24% with unstable angina received all five secondary prevention therapies at discharge (aspirin, clopidogrel, β-blocker, angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker, and statin). Among 2428 cases of PCI performed with stent implantation in seven Melbourne hospitals between April 2004 and December 2005, DES was used in 45% of cases, of which 88% involved patients with diabetes, small vessels, long lesions, in-stent restenotic lesions, chronic total occlusions and bifurcation lesions.[49] The indications and outcomes for PCI in this study are yet to be reported.

Using registries to monitor real-world outcomes and to complement clinical trials

Although randomised trials will (and should) remain the gold standard for determining PCI efficacy, extrapolating trial results to routine practice in interventional cardiology is limited by:

- selection bias, with the frequent exclusion from trials of high-risk patients with complex disease, who may benefit from PCI;
- inferior comparators as rapid changes in PCI technology outpace fixed protocols of trials that may span several years;
- insufficient power of trials to discern variations in PCI effects among different patient subgroups or clinical settings, or to identify long-term hazards;
- limited generalisability of results achieved in PCI centres of excellence participating in trials; and
- clinician misperception of benefit due to conflation of patient-critical endpoints (avoidance of death or re-infarction) with quality-of-life endpoints (avoidance of TVR as a marker of angina-free status) within composite outcomes.

A strong case can therefore be made for a large-scale, prospective registry of PCI that is able to longitudinally track patient outcomes in relation to baseline patient characteristics, indications for intervention, coronary anatomy, procedural technique and site of care (Box). Undertaken at a national level using standardised definitions and datasets, such a registry could detect trends towards adverse outcomes and variations in PCI use that may warrant reassessment of its use in specific circumstances (as a form of "post-marketing surveillance") and facilitate monitoring and benchmarking of PCI performance. Calls have been made for the establishment of a national cardiac procedures registry,[50] but, apart

from preliminary work in data definition, no further action has been taken.

There is an urgent need for both government and professional advocacy in this area: governments need to provide infrastructure support and funding for the establishment and maintenance of such registries; and interventional cardiologists need to design and populate the registry with complete and accurate datasets, and alter practice according to its findings. Expecting patients and funders to continue supporting unrestricted and unmonitored use of costly PCI in situations where efficacy and safety concerns remain unresolved is clearly undesirable, and the creation of a national PCI registry should now proceed without further delay.

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Competing interests

None identified.

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