Impact of operator volume for percutaneous coronary intervention on clinical outcomes: what do the numbers say?

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The impact of operator and centre volume on clinical outcomes and quality of care has been of considerable debate in recent years in a number of surgical- and procedural-based specialities. A relationship between higher volumes at both the institutional and operator levels and better clinical outcomes would at first appear intuitive, based on the premise that performing a procedure very infrequently would be likely to lead to unfamiliarity, complications, and poorer outcomes. In the current review, we study the relationship between operator volume and outcomes in the setting of percutaneous coronary intervention (PCI), and examine the evidence for current clinical competency guidelines that advocate that a minimum number of PCI procedures be undertaken annually. Whilst both high institutional and operator volumes have been shown to be associated with better outcomes by reducing death and in-hospital mortality, these data are often derived from the pre-stent era, or when high-volume operators undertook far smaller numbers of procedures than is currently recommended to maintain clinical competency. The emphasis of specific volume requirements for optimal outcomes needs to be interpreted with caution, as volume is not a surrogate for quality and merely one of the variables associated with outcome. Healthcare providers should focus on other measures of quality such as robust clinical care pathways, evidence-based treatments, periodic case review, using validated risk assessment scores, and ascertainment of outcome to improve care and reduce adverse events.

Keywords
Percutaneous coronary intervention • Operator volume • Centre volume • Outcomes

Introduction

The impact of operator and centre volume on clinical outcomes and quality of care has been of considerable debate in recent years in a number of surgical- and procedural-based specialities. In the setting of percutaneous coronary intervention (PCI), this has been driven in part, by the expansion of both the number of institutions and of individual operators undertaking such procedures and secondly by the decline in the total number of PCI procedures performed in certain countries.1 This has been reflected in a decline in procedural volumes at both the operator and institutional levels.

A relationship between higher volumes at both the institutional and operator levels and better clinical outcomes would at first appear to be intuitive, based on the premise that performing a procedure very infrequently would be likely to lead to unfamiliarity, complications, and poorer outcomes. Previous studies have suggested that low operator/institutional volume may be associated with an increased risk of adverse events in the PCI setting.2–4 The current American College of Cardiology, American Heart Association and Society for Cardiovascular Angiography and Intervention (ACC/AHA/SCAI) clinical competency guidelines recommend minimum requirement of 50 interventional procedures per year (averaged over 2 years) to maintain competency5 with Class C level of evidence, reduced from previous older recommendations derived from the same professional bodies of 75 procedures per year.6 In the UK, the British Cardiovascular Interventional Society (BCIS) advocates that independent operator should perform a total of 150 procedures over 2 years to maintain competency7 with similar recommendations from the ESC guidelines giving a Class Ila evidence level C recommendation for individuals undertaking PCI for acute coronary syndromes (ACS).8
In this review, we sought to assess the evidence behind such recommendations and the relationship between operator volume and clinical outcomes in the setting of PCI.

**Operator volume relationship with major outcomes**

Traditionally, the benchmark outcomes used to define successful PCI are mortality (in-hospital and 30 days), unplanned Coronary artery bypass graft (CABG) (same day, same stay, urgent, or elective), and neurological events such as stroke, TIA, myocardial infarction, and major contrast reactions.

A number of studies have reported the association of volume with mortality in PCI and CABG. For instance, Hannan et al. investigated the mortality in different volume operators for CABG and found that high-volume surgeons have lower risk-adjusted mortality rates. Various observational studies have also reported variable volume–mortality relationships in PCI setting with studies showing both an association with increased operator volumes and better outcomes and no effect.

Table 1 represents an overview of key studies investigating the association between operator volumes and clinical outcomes.

An analysis of 457,498 PCI procedures performed in the United States between 2005 and 2009 illustrated that crude mortality rates decreased with increasing annual operator volume, with crude mortality rates of 1.68, 1.15, 0.87, and 0.59% in 1st (≤15 PCIs/y), 2nd (16–44 PCIs/y), 3rd (45–100 PCIs/y), and 4th (≥100 PCIs/y) quartiles of operator volume. Following adjustment for differences in baseline co-variates, patients treated by the lowest quartile of operator volume, odds ratio (OR) of mortality for the patients treated by 2nd, 3rd, and 4th quartile of operator volume were 0.80 (0.74–0.87, \( P < 0.001 \)), 0.81 (0.74–0.89, \( P < 0.001 \)), and 0.65 (0.58–0.73, \( P < 0.001 \)), respectively. Interestingly, the authors of this study report a cut-off, whereby further increases in operator volume do not reduce predicted mortality, with predicted probability of mortality decreased with increasing operator volume but flattening at ≈300 procedures per year. Minges et al. studied hospital mortality in 3649 physicians who performed 345,526 PCIs. After multivariable adjustment, in-hospital mortality was significantly higher among physicians performing <75 PCIs/year (OR 1.14; 95% CI 1.05–1.24).

However, the absolute difference in mortality was only 0.3%. Mosucci et al. undertook a study of 18,504 consecutive PCIs performed by 165 operators in a regional registry based in Detroit, and reported that the unadjusted major adverse cardiovascular event (MACE) rate was significantly higher in the group of patients treated by the lowest-volume operators (Quartiles 1 and 2) when compared with the group of patients treated by the highest-volume operators (Quartile 5). This persisted after adjustment for differences in baseline co-variates (adjusted OR 1.63, 95% CI 1.29–2.06, \( P < 0.0001 \) for Q1 vs. Q5; adjusted OR 1.63, 95% CI 1.34–1.90, \( P < 0.0001 \) for Q2 vs. Q5). Interestingly, no relationship between in-hospital mortality and operator volume was documented in this cohort of patients once differences in baseline covariates were adjusted for. When operators were stratified according to whether they met the 75 case annual operator volume recommendations made by the ACC/AHA at the time of publication of the paper, MACE and mortality risks were similar in patients treated by operators performing <75 PCIs/year when compared with the group of patients treated by operators performing ≥75 PCIs/year (adjusted OR for death 0.81, 95% CI 0.47–1.41, \( P = 0.46 \); adjusted OR for MACE 1.05, 95% CI 0.83–1.32, \( P = 0.67 \)).

A recent meta-analysis of 23 studies evaluating 15,907 operators performing 205,214 PCIs that predated the largest analysis to date by Badheka et al., illustrated that operator volume was not related to mortality (OR 0.96, 95% CI 0.86–1.08), although they reported a decrease in MACE comparing high- with low-volume operators with an odds ratio of 0.62 (95% CI 0.40–0.97). A limitation of this meta-analysis was that the definitions of high- and low-volume operators varied across studies, with studies comparing outcomes between operators undertaking ≥11 PCI procedures to those undertaking 1–2 annually and those comparing outcomes of operators undertaking ≥100 procedures annually with those <100 procedures pooled, resulting in significant heterogeneity.

The variable relationships reported between operator volumes and outcomes in PCI may relate to a number of factors. Studies have not adjusted for differences in patient co-variates or failed to adjust for time trends that may influence outcomes independently of operator volumes. Most studies have not adjusted for hospital volumes and much of the available evidence stems from the pre-stent era of PCI. Furthermore, even in the largest, most contemporary analysis to date by Badheka et al., data relating to procedural and lesion characteristics were not available and half the PCIs undertaken during this period were excluded due to missing unique operator identification numbers which will have potentially introduced significant bias. In three of the most contemporary/largest studies that have focussed on operator volume outcomes, case-mix adjustment has been performed through inclusion of potential confounding factors in regression models. It is important to distinguish between confounders and mediators: it is not appropriate to correct analyses for procedural decision variables, as these may be consequences of the experience of the operator or centre; all studies considered appropriately did not consider such variables. All studies also accounted appropriately for clustering at the centre level—through inclusion of random effects or generalized estimating equations. There are some limitations in the approaches used in existing studies. One is that volume is either dichotomized or categorized, rather than considering volume as a continuous variable and allowing non-linear effects (Badheka et al. do consider splines, but only in their univariable modelling). A second limitation is in the definition of volume itself, which is taken is the number of procedures performed in the current calendar year. Therefore, procedures performed early in a year have outcomes that are predicted based on future volume. An alternative would be to define volume on a procedure-by-procedure basis, as the number of procedures performed over the previous 12 months. Finally, a common problem in the existing analyses is that the highest-volume category reported tends to underestimate the actual procedure volumes, since that category is open ended and its reference point is the lowest volume in the range. This can be particularly problematic when these data are used to estimate volume thresholds that are being recommended to achieve desired outcomes.
<table>
<thead>
<tr>
<th>Study ID</th>
<th>Design; year; country</th>
<th>Data source</th>
<th>No. of PCIs</th>
<th>No. of centres/No. of operators</th>
<th>Operator PCI volume</th>
<th>Clinical outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hannan 1997</td>
<td>Retrospective; 1991–94; USA</td>
<td>Coronary angioplasty reporting system of New York State</td>
<td>62,670</td>
<td>31/NA</td>
<td>&lt;75 vs. ≥ 175 PTCA/year</td>
<td>In-hospital mortality: OR 0.84 (95% CI 0.67–1.07). Same-stay CABG: OR 3.93 (95% CI 3.65–4.24).</td>
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<td>Ellis 1997</td>
<td>Prospective; 1993–94; USA</td>
<td>PCI dataset from 5 high-volume interventional centres, Cleveland, OH, USA</td>
<td>12,985</td>
<td>5/NA</td>
<td>≤ 70 vs. &gt; 270/year</td>
<td>MACE: OR 0.31 (95% CI 0.28–0.35) Both death and the composite adverse outcome were strongly and inversely related to the number of cases each operator performed annually, but showed no relation to the total number of years of physician experience.</td>
</tr>
<tr>
<td>Malenka 1999</td>
<td>Prospective; 1994–96; USA</td>
<td>Northern New England PCI dataset.</td>
<td>15,080</td>
<td>5/47</td>
<td>84 vs. ≥ 138 PCI/year</td>
<td>In-hospital mortality: OR 1.27 (95% CI 1.05–1.54). No significant relation between operator volume and MACE.</td>
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<tr>
<td>McGrath 2000</td>
<td>Retrospective; 1997; USA</td>
<td>Medicare National Claims, USA</td>
<td>167,208</td>
<td>1003/6534</td>
<td>&gt; 60 vs. &lt; 30 PCI/year</td>
<td>In-hospital mortality: OR 0.96 (95% CI 0.89–1.02) Risk of CABG (&lt; 30 PCI/year): 2.25 vs 1.55% (&gt; 60 PCI/year).</td>
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<td>Vakili 2003</td>
<td>Retrospective; 1995; USA</td>
<td>Coronary angioplasty reporting system of New York State</td>
<td>1342</td>
<td>32/151</td>
<td>&lt;75 vs. ≥ 75 PCI/year</td>
<td>In-hospital mortality: OR 0.82 (95% CI 0.19–3.60).</td>
</tr>
<tr>
<td>Harjai 2004</td>
<td>Retrospective; 1991–2001; USA</td>
<td>Beaumont PCI dataset</td>
<td>12,293</td>
<td>1/28</td>
<td>≤ 92 vs. &gt; 140 PCI/year</td>
<td>In-hospital mortality: OR 1.26 (95% CI 0.72–2.19) No relation between operator volume and composite endpoint (death, CABG surgery, myocardial infarction, or stroke).</td>
</tr>
<tr>
<td>Hannan 2005</td>
<td>Retrospective; 1998–2000; USA</td>
<td>Coronary angioplasty reporting system of New York State</td>
<td>107,713</td>
<td>34/263</td>
<td>&lt;75 vs. ≥ 75 PCI/year</td>
<td>In-hospital mortality: OR 0.77 (95% CI 0.58–1.02) For an operator volume threshold of 75 PCIs/year, same-day CABG OR 1.65 (95% CI 1.05–2.60) and same-stay CABG OR 1.55 (95% CI 1.10–2.18).</td>
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<tr>
<td>Moscucci 2005</td>
<td>Prospective; 2000; USA</td>
<td>University of Michigan regional consortium</td>
<td>18,504</td>
<td>14/165</td>
<td>&lt;75 vs. ≥ 75 PCI/year</td>
<td>In-hospital mortality: OR 0.81 (95% CI 0.47–1.41) MACE: OR 1.05 (95% CI 0.83–1.32) However, when operator volume divided into quintiles (1–33, 34–89, 90–139, 140–206, and 207–582 PCIs/year). Patients treated by low-volume operators had a 63% increased odds of MACE (adjusted OR 1.63, 95% CI 1.29–2.06, for Q1 vs. Q5; adjusted OR 1.63, 95% CI 1.34–1.90, for Q2 vs. Q5).</td>
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<td>Cantor 2006</td>
<td>Retrospective; 1995–2001; Canada</td>
<td>Ontario, Canada</td>
<td>38,561</td>
<td>8/65</td>
<td>&lt;155 vs. &gt;195 PCI/year</td>
<td>30 days mortality: OR 1.30 (95% CI 1.03–1.63) There was no significant difference influence of operator volume on same-stay CABG.</td>
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Table I

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<td>Politi 2006</td>
<td>Retrospective; 2004–5; USA</td>
<td>Como, Italy</td>
<td>331</td>
<td>1/3</td>
<td>63 vs. 82 PCI/year</td>
<td>In-hospital mortality; OR 1.07 (95% CI 0.35–3.26)</td>
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<tr>
<td>Xie 2008</td>
<td>Retrospective; 1996–99; USA</td>
<td>Coronary angioplasty reporting system of New York State</td>
<td>124 218</td>
<td>34/233</td>
<td>&lt;75 vs. 75–174 PCI/year</td>
<td>In-hospital mortality; OR 0.74 (95% CI 0.58–1.02)</td>
</tr>
<tr>
<td>Madan 2009</td>
<td>Retrospective; 1999–2000; USA and Canada</td>
<td>Participants from ESPRIT trial</td>
<td>1338</td>
<td>31/57</td>
<td>&lt;100 vs. ≥ 100 PCI/year</td>
<td>30 days mortality; OR 1.02 (95% CI 0.93–1.12)</td>
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Operator volume and its association with outcomes in primary percutaneous coronary intervention

Primary percutaneous coronary intervention (PPCI) is considered the current gold standard reperfusion therapy in patients presenting with ST-elevation myocardial infarction (STEMI). A number of studies have examined the relationship between PPCI interventionist annual volume and adverse outcomes. Two studies have shown significant impact of operator volume on in-hospital mortality, although these should be interpreted with caution as they analysed data from the mid-1990s and 2000–2, with high-volume operators defined as having performed ≥11 procedures annually or ≥10 procedures annually. Conversely, a third study based on a single centre containing three operators observed no relationship between operator volume and outcome. Interestingly, the study of Srinivas examined PPCI outcomes in New York State examined the capacity of high-volume physicians to offset the risks of low-volume hospitals and vice versa by modelling their interactions. The estimated OR for operator volume categories stratified by low- and high-volume hospitals demonstrated no significant difference in outcome between high- and low-volume physicians (≥10/ year vs. <10/year) in hospitals performing ≥50 primary PCIs/year (OR 1.44, 95% CI 0.68–3.03). However, in hospitals performing ≥50 primary PCIs/year, high-volume physicians had significantly lower risk-adjusted mortality compared with low-volume operators (>0.58, 95% CI 0.39–0.86), suggesting an interaction between operator volume and institutional volumes and outcomes. A number of limitations exist when attempting to interpret data from such studies with currently measured metrics of system-wide quality, such as door-to-balloon time, unavailable to the authors. Hence, the extent to which volume-related differences in outcome were confounded by delays in treatment and other processes of care is unclear.

Further work is needed to unpack the relationship between volumes and outcomes in the context of PPCI. However, in light of the existing evidence, the AHA has recommended that operators should perform a minimum of 11 PPCI per year to maintain competency. BCIS on the other hand has recommended that operators participating in PPCI cases should undertake an absolute minimum of >50 elective/emergency cases/annum within the emergency PCI site and a total workload of at least 120 PCI cases plus up to 30 interventional diagnostic procedures.

PCI volume and outcomes in different settings

Procedural aspects of PCI and their success may also relate to volumes of procedure undertaken. For example, data derived from the RIVAL (Radial vs. femoral) trial that randomized 7021 patients with ACS to radial vs. femoral access for PCI, suggest that procedural radial volumes may impact on PCI outcomes associated with the TRA utilization. Whilst in the subgroup of high-volume radial centres the primary outcome was reduced by adoption of TRA, this was not observed in intermediate- or low-volume radial centres, and furthermore there was no significant interaction by individual operator radial volume. In an analysis of the National Cardiovascular Data Registry (NCDR), there was a clear relationship between volume of chronic total occlusion (CTO) PCI cases and outcomes, with procedural success among operators performing <5, 5–10, and >10 CTO PCI procedures per year was 53, 62, and 75%, respectively (P < 0.001), although MACE rates were similar.
Influence of institutional volume on outcomes

In one of the very early studies relating institutional volume with outcomes, Hartz et al. reported a neutral effect of institutional volume on adverse outcomes. Since then numerous other studies have evaluated the relationship between centre volume and adverse outcomes, with several reporting that there is an inverse relation between volume and outcomes, with the study by Badheka et al. suggesting that the relationship between centre volume and inhospital mortality flattened in centres with an institutional volume of ≥1500 procedures a year. Interestingly, this study suggested that the relationship between centre volume and outcomes became statistically non-significant once operator volume was added to the model. Similarly, the hospital volume effect was no longer evident once adjustments were made for other confounding risk factors.

Reported associations between centre volume and clinical outcomes may only apply to higher-risk cases. In an analysis of outcomes derived from 27,965 patients at 67 hospitals, PCI performed at hospitals with a volume of ≥2,000 PCI/year was independently associated with a lower hospital mortality (OR 0.67, 95% CI 0.52–0.87; P = 0.002), although this relationship was only significant in cases undertaken for AMI indications and not elective cases. Similar observations were recorded in the Greater Paris Registry, with an association between high centre volume and decreased in-hospital mortality reported in emergency cases but not in elective cases. A recent meta-analysis of 10 studies comprising 1,322,342 patients in 1,746 hospitals demonstrated that patients treated in high-volume hospitals (≥600 PCI/year) experienced lower in-hospital mortality (OR 0.87, 95% CI 0.83–0.91) compared with patients treated in lower-volume hospitals (400–600 PCI per year). There is some evidence that the disparity in outcomes of PCI between high- and low-volume hospitals has narrowed over time, for example Ho et al. reported a slight attenuation of the volume–outcome relation for PCI, but his finding pertained to the period between 1984 and 1996 with many of the studies derived from the pre-stent era, with more contemporary data reporting such temporal changes not available. Finally, there may be a centre size over which clinical outcomes become compromised. For example, a lot of discussion has focussed around the development of high-volume mega-centre primary PCI programmes with potential drawbacks raised that an overload of functional/ischaemia led revascularization. Furthermore, with the advent in primary PCI, the requirement to run a primary PCI rota has added to the desire to increase operator numbers per centre, where there is a balance between safe on-call rotas, and enough PCI activity to maintain higher-volume operators. These factors have contributed to decrease in operator volumes over time that has renewed interest in the relationship between operator volume and outcomes. Volume is often used as surrogate for quality measurement as it is easily measureable, and earlier studies showed correlation of outcomes at both operator and centre levels. Many of these earlier studies were limited by the definitions of what a high- or low-volume operator constituted, with several of the early studies defining high-volume operators having undertaken ≥1,000 procedures per year. Several studies were undertaken in the era before stents became routinely used in PCI; hence, their ability to inform contemporary practice where PCI is undertaken in more complex patients is unclear. Furthermore, studies that have focussed on the association between centre volume and outcomes from an institutional perspective, have suggested that such relationships may only apply to higher-risk cases undertaken in the acute situation and not elective cases, although it is not known whether such associations similarly apply at the level of the individual operator.

Some more recent studies seem to suggest that high-volume operators outperform low-volume operators especially in reducing adverse outcomes, although the recent evidence regarding hospital-level volume is less clear. ’Selective referral’ phenomenon may be one plausible explanation of the operator-level findings, i.e. better performing physicians attract more referrals, although it is unlikely that such a phenomenon may influence centre choice in the PPCI setting where decisions regarding treatment centre choice are based on locality. The studies that have found evidence of a centre-level effect may have more favourable outcomes in higher volumes because they simply have better care pathways, more structured and streamlined protocols and practice more evidence base treatments which in turn improve outcomes. For example, in the study by Srinivas et al., higher-volume centres were more likely to follow evidence-based guidelines, whilst Thiemann et al. reported that using better care and proven care pathways reduces mortality in patients admitted with AMI in high-volume centres. It is also important to understand whether working at high-volume centres have any influence on outcomes at physician level, which may relate to operator skill and practice being influenced by their working environment.

It is important to understand the disparities of operator volume–outcome analyses at regional and international levels. Geographical variation of PCI volume may explain dissimilarities in the volume–outcome relationships reported in the literature, as the definition of high-volume centre in one country may not represent the high volume in another country. For instance, the optimal minimum case-load requirements of 400 PCI per facility were only met by 51% of US centres in 2012 and in fact one-third of the centres performed...
<200 PCIs per year,

whereas in UK only 22% centres had a case-load of <400 per year with only 2 centres performing <200 PCIs per year.41 Such differences in individual volumes from both the centre and operator perspective and differences in mortality outcomes across different countries may mask any volume–outcome relationships. For example, in countries with very high caseload of PCIs at the individual operator/centre and lower mortality rates, or conversely in those countries where the vast majority of PCIs are undertaken at low-volume centres/operators and with higher mortality rates, volume–outcome relationships might not be observed. One needs to carefully consider the differences in local PCI practices, centre and operator volume, and geographical variations in PCI-related mortality before translating these results into local practice.

Volume outcome analyses can be used for benchmarking performance both at individual operator and centre levels, particularly in the move towards national transparency agendas in many countries with public reporting of individual operator and centre outcomes. Such volume outcome analyses are useful in assessing quality changes when the delivery of services is restructured, with a recent analysis from Denmark demonstrating that doubling the capacity of a PCI centre due to merger of services was feasible without compromising the quality of care parameters of in-hospital delays, epicardial reperfusion rate and 30-day mortality.34 Such work may help define optimal catchment areas for restructured services, and benchmarks to drive quality improvement and clinical outcomes.

An important limitation of current data is of lack of evidence on interplay between volume–outcome and lifetime experience of operator. In current era, lifetime operator experience is an important metrics as senior cardiologists have overseen more than three decades of advancement of technology and practices in PCI from balloon angioplasty to new generation bioabsorbable stents. It is perhaps logical to think that lifetime learning and years of experience may play an important role in reducing adverse events and complications as well as simply the annual volume of operators. To date, lifetime experience has not been systematically studied in the PCI setting; however, an observational analysis of the UK National Cardiac Surgery Audit studying in-hospital mortality in 292 973 CABG procedures undertaken by 273 surgeons suggests that crude mortality increased approximately linearly until 33 years’ service.32 Despite adjustment for adverse clinical and procedural characteristics and year of surgery, there remained a statistically significant (P = 0.002) association between length of service and in-hospital mortality (OR 1.013, 95% CI 1.005–1.021 for each year of ‘experience’). This might suggest unmeasured confounding or a real association between adverse outcomes and length of service. Finally, as the techniques for PCI have become much more standardized, with advancements in stent technology that has improved the deliverability and performance of stents, with the development of dedicated equipment that enables more complex PCI procedures to be completed more easily, the PCI procedure may have become less dependent on the skills of the individual operator and more so influenced by advances in technology and equipment. Consequently volume–outcome relationships, particularly at the individual operator (or centre) level may be a dynamic relationship, which is likely to be particularly evident for new procedures but as the procedure becomes more routine, and technological advances become more important such relationships will be minimized. Indeed, in support for such a view, some studies have reported that the disparity in outcomes of PCI between high- and low-volume hospitals has narrowed over time.33 Furthermore, as procedures become more routine, volume outcome relationships might only persist for more complex procedures such as CTOs as outlined above27 or in non-elective higher-risk cases.23 Consequently for benchmarking and quality improvement initiatives, volume outcome relationships may become moving targets, inextricably linked with the technological and equipment advances that reduce the challenging nature of cases and entry of the procedure being assessed into routine care.

Conclusion

Both high institutional and operator volumes have been shown to be associated with better outcomes by reducing death and in-hospital mortality, although these data are often derived from the pre-stent era, or in higher-risk patient cohorts. The emphasis of specific volume requirement needs to be interpreted with caution, as volume is not a surrogate for quality and merely one of the variables associated with outcome. The variation in volume–outcome relationship between the countries may also make it difficult to translate the results into local practice. Healthcare provider should also focus on other measures such as robust clinical care pathways, evidence-based treatments, periodic case review, using validated risk assessment scores, and ascertainment of outcome to improve care and reduce adverse events. Furthermore, relative benefits of better outcomes in the context of high-volume centres need to be carefully weighed against the risks of reducing availability of PCI to wider population.

Conflicts of interest: None declared.

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