cardiovascular events and should, therefore, be treated to the aggressive goals of <70 mg/dl for LDL cholesterol, and <100 mg/dl for non-HDL cholesterols, even if a statin at the highest dose increases the risk of adverse effects. However, caution should be employed with elderly patients and individuals with chronic kidney disease, who are more likely to develop adverse effects.

> “...nonstatin therapy added to statin monotherapy failed to improve outcomes...”

In the National Cholesterol Education Program Adult Treatment Panel III Guidelines, target levels of LDL cholesterol and non-HDL cholesterol are established on the basis of classification of risk of cardiovascular disease, but patients are not restricted to specific drug strategies.[8] Consequently, combination therapy with a statin and a nonstatin drug is recommended in these guidelines for the treatment of dyslipidemia, if the target levels of cholesterol are not achieved with statin monotherapy. However, randomized, controlled trials have led to a clinical quandary. Although titration to the highest dose of a statin has been associated with an increased risk of adverse effects, as discussed above, nonstatin therapy added to statin monotherapy failed to improve outcomes in the ACCORD[9] (Action to Control Cardiovascular Risk in Diabetes) and AIM-HIGH[10] (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health) trials. In the ACCORD trial,[9] the addition of fenofibrate to statin therapy in patients with type 2 diabetes and a high risk of cardiovascular disease failed to reduce the risk of fatal cardiovascular events. In the AIM-HIGH trial,[10] niacin added to statin therapy in patients with low HDL cholesterol also failed to improve the incidence of cardiovascular events.

In summary, for patients receiving a high dose of a statin and with excessive levels of non-HDL cholesterols, clinicians must consider the risk–benefit ratio of titration to the highest dose of the statin, or addition of a second drug, which does not yet have documented outcome benefits. This decision needs to be made after balancing the risk of a future cardiovascular event, because of inadequate lipid control, against the adverse effects of the highest dose of a statin, which are more likely to occur in elderly patients or those with renal or hepatic impairment.

The University of Chicago Pritzker School of Medicine, 515 North State Street, Suite 2700, Chicago, IL 60654, USA
mdavidsonmd@gmail.com

Competing interests
The author declares no competing interests.

1. Preiss, D. *et al.* Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. *JAMA* **305**, 2556–2564 (2011).
2. Sattar, N. *et al.* Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. *Lancet* **375**, 735–742 (2010).
3. Rajpathak, S. N. *et al.* Statin therapy and risk of developing type 2 diabetes: a meta-analysis. *Diabetes Care* **32**, 1924–1929 (2009).
4. Sampson, U. K., Linton, M. F. & Fazio, S. Are statins diabetogenic? *Curr. Opin. Cardiol.* **26**, 342–347 (2011).
5. Ridker, P. M. *et al.* Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N. Engl. J. Med.* **359**, 2195–2207 (2008).
6. Baigent, C. *et al.* Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet* **366**, 1267–1278 (2005).
7. Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) Collaborative Group *et al.* Intensive lowering of LDL cholesterol with 80 mg versus 20 mg simvastatin daily in 12,064 survivors of myocardial infarction: a double-blind randomised trial. *Lancet* **376**, 1658–1669 (2010).
8. US Department of Health and Human Services. *Third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation and treatment of high blood cholesterol in adults (Adult Treatment Panel III) Final Report* [online], http://www.nhlbi.nih.gov/guidelines/cholesterol/atp3full.pdf (2002).
9. ACCORD Study Group *et al.* Effects of combination lipid therapy in type 2 diabetes mellitus. *N. Engl. J. Med.* **362**, 1563–1574 (2010).
10. AIM-HIGH Investigators. The role of niacin in raising high-density lipoprotein cholesterol to reduce cardiovascular events in patients with atherosclerotic cardiovascular disease and optimally treated low-density lipoprotein cholesterol. Rationale and study design. The Atherothrombosis Intervention in Metabolic syndrome with low HDL/high triglycerides: Impact on Global Health outcomes (AIM-HIGH). *Am. Heart J.* **161**, 471–477 (2011).

INTERVENTIONAL CARDIOLOGY

How should the appropriateness of PCI be judged?

Gregg W. Stone and Jeffrey W. Moses

The appropriateness of percutaneous coronary intervention in the US has been examined from a large database of more than 500,000 procedures. The findings are surprising and, given their potential to be applied to quality-improvement initiatives, peer-review, and possibly reimbursement decisions, the proper interpretation of these results is essential.

Stone, G. W. & Moses, J. W *Nat. Rev. Cardiol.* **8**, 544–546 (2011); published online 6 September 2011; doi:10.1038/nrcardio.2011.135

Every day more than 2,000 patients in the US undergo percutaneous coronary intervention (PCI), usually with the permanent implantation of one or more coronary stents. Few would argue that PCI is life-saving in patients with acute or imminent coronary occlusion, and substantially improves quality of life in patients with severe angina. Conversely, although procedural complications, stent thrombosis, and late restenosis have become relatively uncommon with the latest generation of devices,[1] the occurrence of these adverse effects can have serious consequences, and interventional cardiology procedures contribute substantially to the health-care budget. Thus, responsible physicians carefully weigh the likelihood that patients will benefit from such procedures. How are these decisions made?

Approximately 30 years ago, physicians largely relied upon experience, intuition, and anecdotes to guide patient care. Since that time, we have entered an era of ‘evidence-based medicine’, characterized by reliance on randomized trials and observational studies to guide clinical decision-making. Professional societies expend great effort to synthesize thousands of studies into exhaustive clinical guidelines. However, many clinical scenarios are not directly addressed by the guidelines. From this void, ‘appropriateness use criteria’ (AUC) have emerged, in which diagnostic and therapeutic procedures for a range of typical patient presentations are categorized on an ordinal scale as ‘appropriate’, ‘uncertain’, or ‘inappropriate’.[2] In 2009, a 17-member, expert panel of multispecialty physicians and researchers plus one

health-insurance officer chose 198 distinct clinical indications (from more than 4,000 possibilities) and adjudicated the appropriateness of coronary revascularization on the basis of combinations of clinical symptom acuity, symptom severity, extent of ischemia, select high-risk clinical features, number of antianginal medications, and the extent of anatomical coronary artery disease.[2]

These AUC have now been used by Chan *et al.* to assess the appropriateness of PCI as performed in 1,091 US hospitals from data abstracted from the National Cardiovascular Data Registry (NCDR) CathPCI Registry.[3] From 602,781 PCIs for which data were submitted to the NCDR between July 2009 and September 2010, adequate descriptive elements were available to classify 500,154 procedures (83.0%). The vast majority of PCIs performed in patients with acute coronary syndromes (ACS, including ST-segment elevation myocardial infarction [STEMI], non-STEMI, and high-risk unstable angina) were considered appropriate, with little interhospital variability, whereas higher percentages of PCI procedures in patients without ACS were considered uncertain or inappropriate (Table 1). In patients without ACS, the interhospital range of inappropriate procedures was wide, varying from 0% to 55% (median 10.8%).[3] How should these data be interpreted?

Table 1 | Appropriateness of PCI procedures in the US[3]

PCI indication	'Appropriate'	'Uncertain'	'Inappropriate'	Total
ACS	350,469 (98.6%)	1,055 (0.3%)	3,893 (1.1%)	355,417
Non-ACS	72,911 (50.4%)	54,988 (38.0%)	16,838 (11.6%)	144,737
Total	423,380 (84.6%)	56,043 (11.2%)	20,731 (4.1%)	500,154

Abbreviations: ACS, acute coronary syndrome; PCI, percutaneous coronary intervention.

> "...the vast majority of PCIs performed in patients with ACS ... were considered appropriate..."

Depending on the perspective, these results can be spun very differently. Some would emphasize that only 4.1% of PCIs in the US are being performed for inappropriate reasons, an extremely small proportion given the variety of clinical and angiographic presentations of coronary artery disease, the variability between hospitals, practitioners, and their local standards, and the lack of scientific evidence to guide all decisions. Even the authors of the AUC note that, for these reasons, a 0% inappropriate rate should not be expected.[2] Conversely, others might opine that nearly half of all nonacute PCI procedures are not being performed for appropriate indications. The proper interpretation of these results has important implications for quality-improvement initiatives, peer-review, and (potentially) reimbursement decisions by medical-insurance payors. Have we entered an era in which individual practitioners, hospital systems, and indeed an entire subspecialty can be graded and judged by such scorecards, thus diminishing or eliminating the need for personalized clinical decision-making?

Understanding the limitations of the AUC and their application as applied through the NCDR is essential to address this issue. First, we can validly question whether the AUC represent an absolute gold standard —are they the final word as to whether PCI should be performed? The AUC were determined using scientific evidence whenever possible, in accordance with the guidelines of the ACC and the AHA. However, only 1 in 10 of these guidelines is based on the highest level of evidence (from multiple randomized trials or meta-analyses); nearly half of the guidelines rely on expert opinion only, without meaningful, supportive scientific studies.[4] Moreover, the opinions of experts vary. Even among the AUC technical panel, only 70–76% agreement existed in the appropriate and inappropriate categories, with wider variation in opinion among the uncertain categories.[2] When a separate panel of 85 cardiologists from 10 institutions reviewed and graded 68 representative indications, their disagreement rate was 66%; no physician achieved uniform concordance with the AUC technical panel.[5] Furthermore, even the authors of the guidelines do not always agree. For example, the ACC/AHA guidelines committee (and the AUC panel) consider PCI performed 12–48 h after the onset of STEMI in an asymptomatic patient to be inappropriate or 'class III' (meaning that it should never be performed, is unhelpful, and might be harmful)[6] whereas, in the European guidelines, which were written by an equally esteemed group of experts after review of the same studies, the same indication is considered to be 'class IIb' (meaning that it can be considered).[7] The majority of the inappropriate NCDR cases after PCI in patients with ACS fell into this category. Equally informed physicians might weigh the implications of nonrandomized studies differently, such as the mortality impact of moderate or severe ischemia in patients with minimal or no angina, which is relieved more effectively by PCI than medical therapy.[8] The 'uncertain' category comprises numerous such examples. Importantly, prospective studies of patient outcomes according to practitioner compliance with AUC have not been performed to confirm the validity of the criteria.

Second, as acknowledged by the AUC panel, <5% of all possible permutations of patient scenarios were classified and scored; many patients do not obviously fall into one of the three predetermined categories. Third, the AUC do not incorporate numerous essential data elements. For example, all stenoses with ≥70% stenosis (or ≥50% stenosis for the left main coronary artery) are considered anatomically important, but neither lesion characteristics nor the amount of myocardium supplied are considered. Few would doubt the great variation in the appropriateness of revascularization of a 95% ulcerated stenosis in a large proximal vessel compared with a 70% smooth stenosis in a small branch. The results of procedural physiological lesion assessment and intravascular ultrasound can substantially affect the appropriateness of PCI, but are not integrated into the AUC decision-making algorithm. Important clinical comorbidities are also not taken into account, such as diabetes mellitus, chronic kidney disease, cerebrovascular disease, or the likelihood of compliance with medications. Neither are patient preferences considered—many patients prefer not to take numerous daily antianginal medications. Fourth, the guidelines and the AUC need to be constantly updated, but this process always lags behind reasonable practice. For example, PCI of left main disease is considered inappropriate by the current PCI AUC (published in 2009 and not yet updated), although the 2008 presentation and 2009 publication of the large-scale, randomized Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) trial[9] resulted in subsequent revisions in both the US and European guidelines, endorsing PCI in selected patients with left main disease. Fifth, hospital data are recorded in the NCDR by persons of varying training and motivation; systemic monitoring of data accuracy

is not undertaken. Finally, neither the AUC[2] nor Chan *et al.*[3] considered the underuse of PCI (and angiography), which might be more harmful than overutilization—for example, resulting in a lack of reperfusion in evolving STEMI.[10]

The authors of the AUC state that "appropriateness criteria are intended to assist patients and clinicians, but are not intended to diminish the acknowledged difficulty or uncertainty of clinical decision-making and cannot act as substitutes for sound clinical judgment and practice experience."[2] The AUC are helpful to identify hospitals and practitioners in whom a closer look at procedural utilization is warranted, with the constructive goal of improving patient outcomes. However, neither the guidelines nor the AUC should be used either as a rubber stamp to sanction procedures or as a sharp knife to castigate a subspecialty consisting of care-givers who grapple every day with complex decisions in the best interests of their patients. Lastly, while outcomes are generally improved by application of guideline-based clinical-care pathways, an excessive reliance on 'cookie-cutter medicine', which requires patients to be shoehorned into preset categories, risks overlooking the unique diagnostic, therapeutic, and social challenges integral to each individual patient that must be considered for medicine to achieve its potential.

*NewYork-Presbyterian Hospital, Columbia University Medical Center and the Cardiovascular Research Foundation, 111 East 59th Street, 11th Floor, New York, NY 10022, USA (**G. W. Stone, J. W. Moses**).*
Correspondence to: G. W. Stone
gs2184@columbia.edu

Acknowledgments
We gratefully acknowledge the insights on this topic provided by Paul S. Teirstein, Scripps Clinic and Research Foundation, La Jolla, CA, USA.

Competing interests
G. W. Stone declares associations with the following companies: Abbott Vascular, Boston Scientific, and Medtronic. J. W. Moses declares associations with the following companies: Boston Scientific and Cordis. See the article online for full details of the relationships.

1. Stone, G. W. *et al.* Everolimus-eluting versus paclitaxel-eluting stents in coronary artery disease. *N. Engl. J. Med.* **362**, 1663–1674 (2010).
2. Patel, M. R. *et al.* CCF/SCAI/STS/AATS/AHA/ASNC 2009 Appropriateness criteria for coronary revascularization: a report by the American College of Cardiology Foundation Appropriateness Criteria Task Force, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, and the American Society of Nuclear Cardiology endorsed by the American Society of Echocardiography, the Heart Failure Society of America, and the Society of Cardiovascular Computed Tomography. *J. Am. Coll. Cardiol.* **53**, 530–553 (2009).
3. Chan, P. S. *et al.* Appropriateness of percutaneous coronary intervention. *JAMA* **306**, 53–61 (2011).
4. Tricoci, P., Allen, J. M., Kramer, J. M., Califf, R. M. & Smith, S. C. Scientific evidence underlying the ACC/AHA clinical practice guidelines. *JAMA* **301**, 831–841 (2009).
5. Chan, P. S. *et al.* Concordance of physician ratings with the appropriate use criteria for coronary revascularization. *J. Am. Coll. Cardiol.* **57**, 1546–1553 (2011).
6. Kushner, F. G. *et al.* 2009 Focused Updates: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 guideline and 2007 focused update) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* **120**, 2271–2306 (2009).
7. Wijns, W. *et al.* Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur. Heart J.* **31**, 2501–2555 (2010).
8. Shaw, L. J. *et al.* Optimal medical therapy with or without percutaneous coronary intervention to reduce ischemic burden: results from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial nuclear substudy. *Circulation* **117**, 1283–1291 (2008).
9. Serruys, P. W. *et al.* Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N. Engl. J. Med.* **360**, 961–972 (2009).
10. Fazel, R. *et al.* Choice of reperfusion strategy at hospitals with primary percutaneous coronary intervention: a National Registry of Myocardial Infarction analysis. *Circulation* **120**, 2455–2461 (2009).