

Meaningful Outcome Measures in Cardiac Surgery

Paul S. Myles, MB BS, MPH, MD, FCARCSI, FANZCA, FRCA

Department of Anaesthesia and Perioperative Medicine, Alfred Hospital, Melbourne, Victoria, Australia;
and the Academic Board of Anaesthesia and Perioperative Medicine, Monash University, Melbourne, Australia

Presented at Winter Meeting Perfusion Downunder 2013, Hayman Island, Queensland, Australia, September 1–3, 2013.

Abstract: The most common cardiac surgical procedures are coronary artery bypass graft surgery and aortic or mitral valve repair or replacement. Underlying conditions include coronary artery disease and heart failure, manifesting as exertional angina, dyspnea, and poor exercise tolerance. The major goals of surgery are to alleviate symptoms and improve patient survival. These, therefore, should inform the choice of primary outcome measures in clinical studies enrolling patients undergoing cardiac surgery. Studies focusing on surrogate outcome measures are relied on all too often. Many are of questionable significance and often have no convincing relationship with patient outcome. Traditional “hard endpoint” outcome measures include serious complications and death with the former including myocardial infarction (MI) and stroke. Such serious adverse outcomes are commonly collected in registries, but because they occur infrequently, they need to be large to reliably detect true associations and treatment effects. For this reason, some investigators combine several outcomes into a

single composite endpoint. Cardiovascular trials commonly use major adverse cardiac events (MACEs) as a composite primary endpoint. However, there is no standard definition for MACE. Most include MI, stroke, and death; others include rehospitalization for heart failure, revascularization, cardiac arrest, or bleeding complications. An influential trial in noncardiac surgery found that perioperative β -blockers reduced the risk of MI but increased the risk of stroke and death. Such conflicting findings challenge the veracity of such composite endpoints and raise a far more important question: which of these endpoints, or even others that were unmeasured, are most important to a patient recovering from surgery? Given the primary aims of cardiac surgery are to relieve symptoms and improve good quality survival, it is disability-free survival that is the ultimate outcome measure. The question then becomes: what is disability and how should it be quantified after cardiac surgery? **Keywords:** outcomes, cardiopulmonary bypass, quality of life. *JECT. 2014;46:23–27*

The most common cardiac surgical procedures are coronary artery bypass graft (CABG) surgery and valve repair or replacement. The two most common underlying conditions are coronary artery disease and heart failure, manifesting as exertional angina, dyspnea, and poor exercise tolerance. It is these symptoms, along with concerns about their own mortality, that bring patients into contact with the cardiac surgical process (1,2). The major goals of surgery are to both alleviate patient symptoms and to improve survival. This reality, therefore, should inform the choice of outcome measures in clinical studies enrolling patients undergoing cardiac surgery. Unfortunately, this is not often the case.

The aim of this review is to consider the range of outcome measures typically included in clinical studies of

patients undergoing cardiac surgery. The growing interest in the use of patient-centered outcomes, the relationship between these and perioperative complications, and the potential value of using disability-free survival as a primary outcome measure are addressed.

SURROGATE OUTCOME MEASURES

A large proportion of clinical studies in patients undergoing cardiac surgery is focused on variables that perhaps help to explain underlying pathophysiological processes during and after surgery and/or surrogate measures that directly or indirectly correlate with true patient outcomes (3–6); for example, measures of cardiovascular performance (cardiac output, vascular resistance, diastolic dysfunction, serum lactate), gas exchange (arterial blood gases), renal function (urine flow, creatinine flux), and inflammation (interleukins, C-reactive protein). Surrogate measures such as these often substitute for true clinical outcomes (7).

Studies focusing on surrogate outcome measures are relied on all too often (3,7). Many are of questionable

Received for publication October 28, 2013; accepted February 1, 2014.
Address correspondence to: Professor Paul S. Myles, Department of Anaesthesia & Perioperative Medicine, Alfred Hospital, Commercial Road, Melbourne, Victoria, 3004, Australia. E-mail: p.myles@alfred.org.au
The author has stated he has reported no material, financial, or other relationship with any healthcare-related business or other entity whose products or services are discussed in this paper.

significance and often have no convincing relationship with patient outcome. For example, a drug proven to lower blood pressure may result in an increased risk of stroke (8), reduce hyperglycemia but increase the risk of death (9), or lower cholesterol but possibly increase the risk of cardiovascular events (10). Efforts to improve surrogate markers of kidney function such as urine flow or reduce biomarkers such as neutrophil gelatinase-associated lipocalin may or may not be valid measurements of renal function or failure (11).

Surgical recovery times and hospital stay reflect both the postoperative course as well as administrative and patient social aspects such as a supportive home environment. Time to tracheal extubation and duration of stay in the intensive care unit (ICU) are common endpoints in cardiac surgical studies. They do provide some indication of the patient's recovery profile and exposure to complications after surgery and are in effect composite measures of the entire perioperative process. They also have social and health economic value; patients want to return home, and the costs associated with prolonged hospitalization can be better spent in other areas. They are, therefore, useful surrogate outcome measures in cardiac surgery. However, they are not sufficient and often do not reflect or evaluate the underlying goals of cardiac surgery. They can also be manipulated.

For CABG surgery and percutaneous coronary intervention, there is genuine interest in the rate of graft occlusion after the revascularization procedure (6). Advances in stent technology and greater understanding of identification of suitable patients, coronary artery anatomy (of lesions), and antiplatelet therapy are aimed at avoiding in-stent thrombosis and early graft occlusions (12). However, an occluded graft is only important if it threatens myocardial viability, and so it can be argued that such endpoints are merely surrogates for recurrence of angina, myocardial infarction (MI), and patient survival (6).

CLINICAL INDICATORS AND REGISTRIES

Clinical indicators are process and outcome measures of both the safety and effectiveness of patient care (13–16). They may also be used to measure surgeon and hospital performance, allowing benchmarking and the identification of many aspects of quality of care. These are best done by adjusting for hospital case mix. With the growing interest in the role of public reporting of outcomes in cardiac, thoracic, and vascular surgery (17–20), procedure registries such as that run by the Society for Cardiothoracic Surgery in the United Kingdom and the Society of Thoracic Surgeons National Adult Cardiac Surgery Database in the United States offer a valuable resource (20,21). However, there are ongoing concerns about clinician and patient privacy, selective reporting, differences in case mix, and

“gaming.” The capacity of the general population to properly evaluate performance and risk is open to question.

Valuable indicators include unplanned reoperation, unplanned ICU admission, and hospital readmission rates. Such outcomes are major setbacks for the patient and have numerous adverse consequences that could include a greater likelihood of poor survival (22). However, few clinical indicators consider the perspective of the patient: are their symptoms relieved and is their life improved?

SERIOUS COMPLICATIONS

Traditional outcome measures include death and serious complications such as MI and stroke. These are uncommon after most types of cardiac surgery, making clinical research more difficult because very large numbers of patients must be enrolled into studies to have sufficient power to detect important differences. For this reason, most researchers combine several outcomes into a single composite endpoint such as major adverse cardiac events (23–25). The use of composite endpoints is problematic and needs to be justified (23). An influential trial in noncardiac surgery found that perioperative β -blockers reduced the risk of MI but increased the risk of stroke and death (26). Such conflicting findings challenge the veracity of such composite endpoints and raise a far more important question: which of these endpoints, or even others that were unmeasured, are most important to a patient recovering from surgery? As stated, recovery times such as ICU and hospital stay mostly reflect a composite of several adverse events after surgery.

POSTOPERATIVE DELIRIUM AND COGNITIVE DYSFUNCTION

Delirium is a common, costly, and potentially serious complication after cardiac surgery. It is more common in the elderly and is associated with an increased risk of death, institutionalization, and possibly dementia (27). Although this is an unwanted scenario after surgery and dose demand extra nursing resources, it is mostly a short-term problem and perhaps related more to the hospitalization and ICU process itself rather than as a surgical-related outcome measure.

Postoperative cognitive dysfunction (POCD) has been frequently studied in cardiac surgery (28–30). Contemporary thinking suggests that POCD is not unique to cardiac surgery involving cardiopulmonary bypass, but in fact occurs at comparable frequency in many types of major surgery (31,32). It may even occur after coronary angiography or in any hospitalized patient with a major medical condition (31). Important aspects of study design for POCD include the use of a recommended test battery, an appropriate control group, and focusing on relative change indices

rather than absolute values (33,34). POCD is defined statistically; it is not based on patient symptoms or their capacity to manage activities of daily living. The subtle changes detected by neuropsychological testing are often not apparent to the patient or their family. There seems to be a relationship between test performance and longer-term outcome (30), but how POCD manifests in a patient's daily life is unclear. POCD is a surrogate measure of mild cognitive impairment and dementia. However, at present, there is insufficient evidence to link POCD and risk of later-onset dementia.

PATIENT-CENTERED OUTCOMES RESEARCH

Rahimi et al. (35) did a systematic review of randomized trials evaluating the treatment or prevention of cardiovascular disease published in 10 leading general medical and cardiology journals from 2005 to 2008. They found that few studies used primary outcome measures that could be rated as important from the patient's point of view. Only 93 of 413 trials (23%) used endpoints such as death or major morbidity or any other patient-reported outcomes. A similar proportion used a composite endpoint that included one or more less important outcomes. They recommended that patients should be directly involved in the selection of meaningful outcome measures for cardiovascular trials. More recent evidence suggests that clinicians sometimes make wrong assumptions about patient preferences and values (36).

These are not new concepts. Chalmers and Clark (37) noted that most large cardiovascular trials use patient survival/mortality as the sole primary endpoint, so-called "tombstone trials." They noted that patients are not only interested in the potential benefits of new treatments on survival, but also how these treatments affect the quality of their lives.

In the United States, the Patient Protection and Affordable Care Act becomes fully implemented in January 2014. The central aim is to reduce costs and improve healthcare outcomes by focusing on quality (rather than quantity) of care. The Patient-Centered Outcomes Research Institute was established as part of this government program with an aim to undertake more comparative effectiveness research (38). These changes place much greater emphasis on outcomes research, evidence synthesis, and knowledge translation, aiming to encourage clinicians to ask about and understand patient preferences to properly inform clinical decision-making.

QUALITY OF RECOVERY AND QUALITY OF LIFE

An overall measure of quality of recovery after surgery is useful in that it can provide a global measure of out-

come from the patient's perspective (39). The 40-item quality of recovery score (QoR-40) has undergone extensive psychometric evaluation (40) and has been used in many cardiac and other surgical studies (41). A systematic review of postoperative recovery outcome measurements found the QoR-40 was the only instrument that fulfilled all of the eight prespecified criteria needed to measure health status: appropriateness, reliability, validity, responsiveness, precision, interpretability, acceptability, and feasibility (42). Other systematic reviews have confirmed its psychometric properties and clinical use (41,43). Quality of life after surgery is also important (44) and is being measured more often in cardiac surgical studies (12,44,45). It is acknowledged that these are important patient-centered outcomes, but some aspects are unrelated to the surgery itself and they may not reflect how well patients can function in the months and years after cardiac surgery.

Patients recovering from major surgery, especially the elderly and those with comorbidity, have a slow and complicated recovery course. They are at increased risk of numerous surgical and medical complications in the weeks and months after surgery. Nearly one-fifth of U.S. Medicare (elderly) patients discharged from the hospital, estimated to be more than 2.5 million people, have an acute medical problem over the next 30 days leading to readmission to the hospital. Krumholz (46) has labeled this phenomenon the posthospital syndrome, and we know this is associated with very poor longer-term survival (47). We simply have insufficient information about what happens to patients in the months after surgery—how many are relieved of their symptoms and go on to enjoy a healthy existence? What proportion are harmed by their surgery?

It is not just survival, but the relief of symptoms, avoidance of long-term disability, and a sense of well-being that are likely to be the most important and highly valued outcomes for patients undergoing major surgery (44,48,49). Disability-free survival, therefore, seems to satisfy the key criteria for an ideal outcome measure after cardiac surgery. It addresses the primary aims of most cardiac surgery: reduced symptoms and/or improved healthy survival. It is clearly a patient-centered outcome. The question then becomes: how would our patients define disability and how should it be quantified after cardiac surgery? Are standard measures of disability such as the Katz activities of daily living (50) and the World Health Organization disability assessment scale (51,52) valid and reliable after surgery? These important questions require urgent study.

REFERENCES

1. Wright RS, Anderson JL, Adams CD, et al. 2011 ACCF/AHA focused update incorporated into the ACC/AHA 2007 Guidelines for the Management of Patients with Unstable Angina/Non-ST-Elevation Myocardial Infarction: A report of the American College

- of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines developed in collaboration with the American Academy of Family Physicians, Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons. *J Am Coll Cardiol.* 2011;57:e215–367.
2. Bonow RO, Carabello BA, Chatterjee K, et al. 2008 focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to revise the 1998 guidelines for the management of patients with valvular heart disease). Endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol.* 2008;52:e1–142.
 3. Fisher DM. Surrogate outcomes: Meaningful not! *Anesthesiology.* 1999;90:355–6.
 4. Goshima KR, Mills JL Sr, Awari K, Pike SL, Hughes JD. Measure what matters: Institutional outcome data are superior to the use of surrogate markers to define 'center of excellence' for abdominal aortic aneurysm repair. *Ann Vasc Surg.* 2008;22:328–34.
 5. Yudkin JS, Lipska KJ, Montori VM. The idolatry of the surrogate. *BMJ.* 2011;343:d7995.
 6. Harskamp RE, Williams JB, Hill RC, de Winter RJ, Alexander JH, Lopes RD. Saphenous vein graft failure and clinical outcomes: Toward a surrogate end point in patients following coronary artery bypass surgery? *Am Heart J.* 2013;165:639–43.
 7. Institute of Medicine. Evaluation of biomarkers and surrogate endpoints in chronic disease. Available at: www.iomedu/Reports/2010/Evaluation-of-Biomarkers-and-Surrogate-Endpoints-in-Chronic-Disease.aspx. Accessed August 26, 2013. 2010.
 8. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: Meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ.* 2009;338:b1665.
 9. Finfer S, Chittock DR, Su SY, et al. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med.* 2009;360:1283–97.
 10. Kastelein JJ, van Leuven SI, Burgess L, et al. Effect of torcetrapib on carotid atherosclerosis in familial hypercholesterolemia. *N Engl J Med.* 2007;356:1620–30.
 11. Cruz DN, Soni S, Ronco C. NGAL and cardiac surgery-associated acute kidney injury. *Am J Kidney Dis.* 2009;53:565–6; author reply 566.
 12. Angelini GD, Culliford L, Smith DK, et al. Effects of on- and off-pump coronary artery surgery on graft patency, survival, and health-related quality of life: Long-term follow-up of 2 randomized controlled trials. *J Thorac Cardiovasc Surg.* 2009;137:295–303.
 13. Haller G, Stoelwinder J, Myles P, McNeil J. Quality and safety indicators in anesthesia: A systematic review. *Anesthesiology.* 2009;110:1158–75.
 14. Major JW, Ibrahim JE, Cicuttini FM, Boyce NW, McNeil JJ. The extraction of quality-of-care clinical indicators from state health department administrative databases. *Med J Aust.* 1999;170:420–4.
 15. Brook RH, McGlynn EA, Shekelle PG. Defining and measuring quality of care: A perspective from US researchers. *Int J Qual Health Care.* 2000;12:281–95.
 16. Peterson ED, Roe MT, Mulgund J, et al. Association between hospital process performance and outcomes among patients with acute coronary syndromes. *JAMA.* 2006;295:1912–20.
 17. Shroyer AL, McDonald GO, Wagner BD, et al. Improving quality of care in cardiac surgery: Evaluating risk factors, processes of care, structures of care, and outcomes. *Semin Cardiothorac Vasc Anesth.* 2008;12:140–52.
 18. Hannan EL, Cozzens K, King SB 3rd, Walford G, Shah NR. The New York State cardiac registries: History, contributions, limitations, and lessons for future efforts to assess and publicly report healthcare outcomes. *J Am Coll Cardiol.* 2012;59:2309–16.
 19. Paul S, Sedrakyan A, Chiu YL, et al. Outcomes after lobectomy using thoracoscopy vs thoracotomy: A comparative effectiveness analysis utilizing the Nationwide Inpatient Sample database. *Eur J Cardiothorac Surg.* 2013;43:813–7.
 20. Bridgewater B. Cardiac registers: The adult cardiac surgery register. *Heart Fail Rev.* 2010;96:1441–3.
 21. Shroyer AL, Coombs LP, Peterson ED, Eiken MC, DeLong ER, Chen A, et al. The Society of Thoracic Surgeons: 30-day operative mortality and morbidity risk models. *Ann Thorac Surg.* 2003;75:1856–64; discussion 1864–5.
 22. Ranucci M, Bozzetti G, Ditta A, Cotza M, Carboni G, Ballotta A. Surgical reexploration after cardiac operations: Why a worse outcome? *Ann Thorac Surg.* 2008;86:1557–62.
 23. Myles PS, Devereaux PJ. Pros and cons of composite endpoints in anesthesia trials. *Anesthesiology.* 2010;113:776–8.
 24. Montori VM, Permyer-Miralda G, Ferreira-Gonzalez I, et al. Validity of composite end points in clinical trials. *BMJ.* 2005;330:594–6.
 25. Kip KE, Hollabaugh K, Marroquin OC, Williams DO. The problem with composite end points in cardiovascular studies: The story of major adverse cardiac events and percutaneous coronary intervention. *J Am Coll Cardiol.* 2008;51:701–7.
 26. Devereaux PJ, Yang H, Yusuf S, et al. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): A randomised controlled trial. *Lancet.* 2008;371:1839–47.
 27. Witlox J, Eurelings LS, de Jonghe JF, Kalisvaart KJ, Eikelenboom P, van Gool WA. Delirium in elderly patients and the risk of postdischarge mortality, institutionalization, and dementia: A meta-analysis. *JAMA.* 2010;304:443–51.
 28. Silbert B, Scott D, Evered L, et al. A comparison of the effect of high- and low-dose fentanyl on the incidence of postoperative cognitive dysfunction after coronary artery bypass surgery in the elderly. *Anesthesiology.* 2006;104:1137–45.
 29. Silbert B, Maruff P, Evered L, et al. Detection of cognitive decline after coronary surgery: A comparison of computerized and conventional tests. *Br J Anaesth.* 2004;92:814–20.
 30. Newman MF, Kirchner JL, Phillips-Bute B, et al. Longitudinal assessment of neurocognitive function after coronary-artery bypass surgery. *N Engl J Med.* 2001;344:395–402.
 31. Evered L, Scott DA, Silbert B, Maruff P. Postoperative cognitive dysfunction is independent of type of surgery and anesthetic. *Anesth Analg.* 2011;112:1179–85.
 32. Hakkinen A, Heinonen M, Kautiainen H, Huusko T, Sulkava R, Karppi P. Effect of cognitive impairment on basic activities of daily living in hip fracture patients: A 1-year follow-up. *Aging Clin Exp Res.* 2007;19:139–44.
 33. Lewis MS, Maruff P, Silbert BS, Evered LA, Scott DA. The influence of different error estimates in the detection of postoperative cognitive dysfunction using reliable change indices with correction for practice effects. *Arch Clin Neuropsychol.* 2007;22:249–57.
 34. Lewis MS, Maruff P, Silbert BS, Evered LA, Scott DA. The sensitivity and specificity of three common statistical rules for the classification of post-operative cognitive dysfunction following coronary artery bypass graft surgery. *Acta Anaesthesiol Scand.* 2006;50:50–7.
 35. Rahimi K, Malhotra A, Banning AP, Jenkinson C. Outcome selection and role of patient reported outcomes in contemporary cardiovascular trials: Systematic review. *BMJ.* 2010;341:c5707.
 36. Mulley AG. Inconvenient truths about supplier induced demand and unwarranted variation in medical practice. *BMJ.* 2009;339:b4073.
 37. Chalmers I, Clarke M. Outcomes that matter to patients in tombstone trials. *Lancet.* 2001;358:1649.
 38. Selby JV, Beal AC, Frank L. The Patient-Centered Outcomes Research Institute (PCORI) national priorities for research and initial research agenda. *JAMA.* 2012;307:1583–4.
 39. Lee A, Lum M. Measuring anaesthetic outcomes. *Anaesth Intensive Care.* 1996;24:685.
 40. Myles P, Weitkamp B, Jones K, Melick J, Hensen S. Validity and reliability of a post-operative quality of recovery score: The QoR-40. *Br J Anaesth.* 2000;84:11–5.
 41. Gornall BF, Myles PS, Smith CL, et al. Measurement of quality of recovery using the QoR-40: A quantitative systematic review. *Br J Anaesth.* 2013;111:161–9.
 42. Herrera FJ, Wong J, Chung F. A systematic review of postoperative recovery outcomes measurements after ambulatory surgery. *Anesth Analg.* 2007;105:63–9.

43. Kluivers KB, Riphagen I, Vierhout ME, Brolmann HA, de Vet HC. Systematic review on recovery specific quality-of-life instruments. *Surgery*. 2008;143:206–15.
44. Cheema FN, Abraham NS, Berger DH, Albo D, Taffet GE, Naik AD. Novel approaches to perioperative assessment and intervention may improve long-term outcomes after colorectal cancer resection in older adults. *Ann Surg*. 2010;253:867–74.
45. Myles P, Viira D, Hunt J. Quality of life at three years after cardiac surgery: relationship with preoperative status and quality of recovery. *Anaesth Intensive Care*. 2006;34:176–83.
46. Krumholz HM. Post-hospital syndrome—An acquired, transient condition of generalized risk. *N Engl J Med*. 2013;368:100–2.
47. Krumholz HM, Lin Z, Keenan PS, et al. Relationship between hospital readmission and mortality rates for patients hospitalized with acute myocardial infarction, heart failure, or pneumonia. *JAMA*. 2013;309:587–93.
48. Myles PS, Hunt JO, Nightingale CE, et al. Development and psychometric testing of a quality of recovery score after general anesthesia and surgery in adults. *Anesth Analg*. 1999;88:83–90.
49. Amemiya T, Oda K, Ando M, et al. Activities of daily living and quality of life of elderly patients after elective surgery for gastric and colorectal cancers. *Ann Surg*. 2007;246:222–8.
50. Ettinger WH Jr, Fried LP, Harris T, Shemanski L, Schulz R, Robbins J. Self-reported causes of physical disability in older people: The Cardiovascular Health Study. CHS Collaborative Research Group. *J Am Geriatr Soc*. 1994;42:1035–44.
51. Guralnik JM, LaCroix AZ, Branch LG, Kasl SV, Wallace RB. Morbidity and disability in older persons in the years prior to death. *Am J Public Health*. 1991;81:443–7.
52. Garin O, Ayuso-Mateos JL, Almansa J, et al. Validation of the ‘World Health Organization Disability Assessment Schedule, WHODAS-2’ in patients with chronic diseases. *Health Qual Life Outcomes*. 2010;8:51.