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Original papers

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Integrating cost-effectiveness evidence into clinical practice guidelines in Australia for acute myocardial infarction

Abstract. A teaching hospital is working with the Victorian State Government and universities, integrating cost-effectiveness evidence into clinical practice guidelines (CPGs), protocols and pathways for respiratory and cardiology interventions. Acute myocardial infarction (AMI) findings are reported. Results will stimulate cost-effective practice and inform medical associations, federal and state governments and international organisations developing CPGs. Published CPGs by the American College of Cardiology/American Heart Foundation for AMI in 1999 are reviewed by a large interdisciplinary hospital-based committee given cost-effectiveness evidence. Levels of evidence criteria rating on methodological rigor for effectiveness and costs are applied. National Health and Medical Research Council (NHMRC) grades of recommendation criteria for combinations of relative effectiveness versus relative costs and cut-off points are used. Extrapolating results between countries was addressed by applying the OECD's health purchasing power parity series. Recommendations for revisions to United States guidelines and for local application are formulated. United States Guidelines require updating: Regarding angioplasty, percutaneous transluminal coronary angioplasty (PTCA) is cost-effective for men aged 60 years relative to recombinant tissue plasminogen activator (tPA), with additional cost per life year saved of 274 ecu. PTCA with discharge after 3 days is cost-effective in low-risk AMI. Regarding GP IIb/IIIa drugs, Abciximab during intervention incurred equal mean hospital costs for placebo, abciximab bolus, and abciximab bolus+ infusion with incremental 6-month cost for the latter treatment costing US$ 293 per patient. Agent recouped almost all initial therapy costs with significant benefits. Incremental cost of abciximab per event prevented is US$ 3,258. Tirofiban was compared to placebo after high-risk angioplasty for AMI or unstable angina. Tirofiban decreased the rate of hospital deaths, myocardial infarction, revascularisation at 2 days by 36% relative to placebo (8% vs. 12%) without increased cost. Clinical benefits were similar at 30 days. Tirofiban+heparin+aspirin was compared to heparin+aspirin. Tirofiban arm resulted in net savings of 33,418 ecu per 100 patients for the first 7 days of treatment. Regarding thrombolytics, tPA is more cost-effective than streptokinase. Incremental costs for each life saved when streptokinase is substituted by recombinant tissue plasminogen are 31%, 45%, 97% higher in Germany, Italy and the United States than in the United Kingdom. Regarding anticoagulants, enoxaparin is a promising alternative to unfractionated heparin for hospitalised patients with non-Q-wave myocardial infarction or unstable angina, saving C$ 1,485 per patient over 12 months with 10% reduction in 1 year risk of death, myocardial infarction or recurrent angina. Regarding anti-arrhymics, the cost-effectiveness of no amiodarone, amiodarone for patients with depressed heart rate variability (DHRV), and amiodarone for patients with DHRV plus positive programmed ventricular stimulation (PPVS) for high-risk post-AMI was investigated. Amiodarone for DHRV+PPVS patients was dominated by a blend of the two alternatives. Compared to no amiodarone, the incremental cost-effectiveness of amiodarone for DHRV patients was US$ 39,422 per quality adjusted life year gained. Amiodarone for DHRV is the most appropriate. Other CPG updates concern serum markers, for example, cardiac troponin I assay (c-TnI), cost advantages of ad hoc angioplasty and secondary prevention through antioxidants and pravastatin. Australian costs are reported later in the paper.

Keywords

Cost-effectiveness · Clinical practice · Guidelines · Acute myocardial infarction

Introduction

Framework for evidence-based medicine in policy and health-care delivery

Evidence-based approaches are prominent on international agendas for health policy and research. Such approaches can impact on three levels: national, intersectoral assessment and in everyday

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medical practice. The potential for priority setting at the national health policy level is limited, and a decentralisation of responsibilities for resource use inevitably occurs. Health care providers assume agency roles for patients and society and are expected to provide cost-effective care [41]. The Australian federal government is facilitating evidence based health policy through requiring evidence of cost-effectiveness before listing and/or reimbursement decisions on new pharmaceuticals, technology and procedural advances. Further, the National Health and Medical Research Council (NHMRC) has developed guidelines for the development of clinical practice guidelines with a strong focus on cost-effectiveness evidence. At the hospital level, published clinical practice guidelines (CPGs) are used extensively to guide decision making for treatment. Further revision of these guidelines in light of recent cost-effectiveness evidence and their integration into pathways and protocols can further stimulate best practice locally. Antioch et al. [9] provide evidence of cost reductions with improved patient outcomes from using some clinical pathways.

A large Australian teaching hospital, The Alfred Hospital, is working with state government and leading Victorian universities integrating cost-effectiveness evidence into CPGs, clinical protocols and clinical pathways and informing medical associations and governments. CPGs are systematically developed statements to assist clinicians, consumers and policy makers to make appropriate health care decisions. Protocols are recommendations to guide physicians, often including a stepwise series of decisions and algorithms. Clinical pathways are multidisciplinary treatment plans specifying patient management through an episode of care.

A large committee, the Clinical Pathways Working Group (CPWG), has led this initiative involving medical, allied health, nursing, economic, policy, information technology, and university academic staff, using the NHMRC guidelines on developing CPGs, along with leading edge international frameworks. Published CPGs for six cardiology and respiratory conditions and procedures are being evaluated given published cost-effectiveness evidence and local cost-effectiveness studies. Recommendations for revised CPGs are developed for inter-disciplinary teams of physicians, nurses and allied health professionals to integrate into the pathways and protocols they construct. Published results will be disseminated to governments and medical associations. This contribution discusses the experience and results of integrating cost-effectiveness evidence into the CPGs for acute myocardial infarction (AMI).

In treating AMI The Alfred Hospital is guided by the American College of Cardiology (ACC)/American Heart Association (AHA) 'Guidelines for the Management of Patients with Acute Myocardial Infarction' [51]. These guidelines are considered the current 'gold standard' by medical cardiology opinion leaders at The Alfred Hospital, given the rigor underpinning their development, date of publication and relevance. We are therefore reviewing these published CPGs and identifying areas for revision based on recent cost-effectiveness evidence and considering their implications for treatment in Australia. Other published CPGs that were initially considered were published by key medical professional associations in Australia, the United States, Europe and Canada.

Several challenges were addressed. Communication between medical, clinical, economic, academic and government experts was facilitated. Acceptable levels of evidence criteria were applied rating economic evaluation on methodological rigor in estimating clinical effectiveness and costs. This principally applied Drummond et al.'s checklist [15] for grading economic evaluation studies.

Acceptable grades of recommendation were applied for adoption of preferred technologies involving combinations of relative effectiveness versus relative costs and choice of cost-effectiveness cut-off points for Australia. Issues in extrapolating results between countries required attention. The CPWG adopted guidelines by the NHMRC [40] for defining cut-off points for grades of recommendation and extrapolating results between countries using the health purchasing power parity. Obtaining consensus in the review methodology and its application was greatly facilitated through sub-committee structures that report to the CPWG.

An overview is presented of the public health significance of acute myocardial infarction (AMI). The USA ACC/AHA guidelines for AMI that were reviewed through this process are then covered, along with an overview of the other guidelines initially considered. This is followed by an outline of the review process used by our Committee for the revisions of the AMI guidelines and clinical protocols and pathways. Level of evidence criterion and grades of recommendation applicable to cost-effectiveness studies are discussed. We then analyse the results of the review of the cost-effectiveness literature on interventions for the treatment of AMI and their implications for the recommendations in the USA guidelines. This covers broad areas relating to angioplasty, glycoprotein (GP) IIb/IIIa antagonist drugs, thrombolytic therapy, anticoagulants and antiarrhythmics. Finally, serum markers and secondary prevention through anti-oxidants and pravastatin are considered.

Public health significance of AMI in Australia and Europe

Cardiovascular disease is the main cause of death in almost all industralised countries. In Australia cardiovascular disease accounted for 42% of deaths in 1996, making it the major cause of premature death and death overall in the country. The WHO MONICA project is an international collaborative project aiming to monitor trends and determinants in cardiovascular disease over a 10-year period. The study has produced event (i.e. occurrence) rate and case-fatality (i.e. death) rate data for acute myocardial infarction (MI) for regions within Australia, Europe, USA and Canada. The Australian sites of Newcastle and Perth ranked in the top 10 of the 20 sites included. The rates of heart attacks were high for the United Kingdom and low for Spain and Italy. Case-fatality was high in the two French study populations.

In Newcastle, Australian men aged between 35–64 years had an event rate of 561 per 100,000 population. The comparable figures for the United Kingdom (Glasgow), Spain (Catalonia) and Italy (Brianza) were 823, 187 and 305 per 100,000 population respectively. The trends for women in the same age group were 188 for Newcastle, 256 for Glasgow, 30 for Catalonia and 48 for Brianza. The

case fatality rates for Newcastle men in the same age group was 43 per 100,000. For the two French study populations it was 58 for Lille and 51 for Strasbourg [10].

American College of Cardiology/ American Heart Association (ACC/AHA) guidelines for AMI

The 1999 ACC/AHA [51] Guidelines for the Management of Patients with Acute Myocardial Infarction are used extensively by The Alfred Hospital for managing AMI patients. These guidelines were therefore selected for the current review in this process. The original guidelines published in 1999 represented the culmination of over 2.5 years of review since their initial publication in 1996 [50] to ensure their continued relevancy. The ACC/AHA indicate that the 1999 update was developed to keep the guidelines current without republishing them in their entirety. The update represented a new procedure of the ACC/AHA Task Force on Practice Guidelines. The guidelines will be reviewed and updated as necessary until it is deemed appropriate to revise and republish the entire document. However, the full text of the guidelines, incorporating the 1999 update, are available on the Web sites of both the ACC (www.acc.org) and the AHA (www.americanheart.org) [51].

The current process of integrating cost-effectiveness evidence-based medicine (EBM) findings into CPG involves the review and update of the ACC/AHA's 1999 guidelines obtained from their websites. An executive summary and recommendations of the ACC/AHA [52] guidelines is also available at the websites of ACC and AHA [52]. This includes an overview of the key recommendations for management of all stages of treatment including prehospital issues, initial recognition and management in the emergency department, hospital management, rationale and approach to pharmacotherapy, preparing for discharge from hospital including secondary prevention. Where new recommendations have been formulated to replace the earlier 1996 recommendations, the old and revised have been juxtaposed.

Several guidelines that were initially considered by the CPWG have been published by the NHMRC [36, 37], American College of Chest Physicians [5], ACC/AHA [51, 52], Society of Nuclear Medicine [54], American College of Physicians and American Society of Internal Medicine [6], Institute for Health Care Quality [25], American College of Radiology [7], European Society of Cardiology, European Atherosclerosis Society, European Society of Hypertension et al. [17], European Society of Cardiology [16], Agency for Health Care Research and Quality [2], ACC/AHA [3], [4] and Canadian Task Force on Preventive Health Care [12].

Cost-effectiveness evidence-based medicine review process

Committee review process

An overview of the processes used by the CPWG in reviewing the clinical practice guidelines, clinical pathways and protocols is outlined below. Steps relating to the review of CPG using cost-effectiveness evidence is consistent with processes identified to date by the NHMRC [40]. This discussion paper represents a key output of the processes outlined below and is being currently used in the development of clinical pathways and protocols for AMI.

Clearly specified clinical governance has proven crucial to The Alfred Hospital's success in the clinical pathway area and has involved keen commitment from senior management and senior clinicians. Our CPWG has responsibility for these processes with reporting lines to the Alfred Executive Committee through its Patient Services and Care Committee and finally to the Chief Executive of Bayside Health Services. CPWG is chaired by a representative from the Office of the Chief Executive, Bayside Health.

The CPWG is a large multidisciplinary committee involving membership of up to 20 members that has involved effective collaboration with Monash, Melbourne and Deakin Universities and the Victorian Government. Key linkages have also been established with world-leading Institutes in Europe. A policy and procedure manual on clinical pathways prepared by the CPWG has been disseminated hospital-wide. We have made much use of the NHMRC [38, 40] materials on the development of clinical guidelines.

Our clinical pathways are developed using the key processes of retrospective clinical data review, mapping out of current practice, use of gold standard published CPG and the integration of best practice cost-effectiveness EBM findings. This involves assessing the need for the clinical pathway, referral to CPWG and selection of all relevant published CPGs in close consultation with medical opinion leaders. Systematic review of the cost-effectiveness literature is undertaken by the CPWG and medical opinion leaders for key related interventions and used to assess CPGs. Compendiums of the EBM review literature are disseminated hospital-wide to key stakeholders, including medical opinion leaders and clinical teams who map out current practice. These teams involve key medical, allied health and nursing practitioners, led by our Clinical Pathway Coordinator.

Brief issues papers identifying the key issues are also disseminated widely. This is followed up by discussion papers that identify the implications of the cost-effectiveness literature for the published CPGs. This is a crucial step as the pathways and protocols developed use the CPGs, and consider necessary revisions, along with the mapping out of current practice. The implications of the evaluated CPGs are integrated into the pathways when final endorsement is sought from leading clinical experts, such as Medical Department Heads. It is also considered at earlier stages when key EBM information is disseminated to the clinical teams. Obtaining consensus in the review methodology and its application was greatly facilitated through subcommittee structures that report to the CPWG. These include EBM authors for AMI with expertise in cardiology (medical, nursing and physiotherapy), health economics and health policy. Other committees include medical, nursing and allied health practitioners who map out current practice in the hospital. Information technology and also clinical pathway evaluation issues are addressed in sub-committees.

The cost-effectiveness literature was reviewed over the period 1997 to 2001 to identify key literature to enable the update of the 1999 AHA/ACC guidelines. This step is considered crucial in Australia given the NHMRC emphasises the need to integrate cost-effectiveness evidence into the development and review of CPGs [38, 40]. The literature review

Table 1
NHMRC criteria: assessing evidence using shadow prices

Ranking of evidence of costs	Ranking of evidence on effects	
	High	Low
Strong	Recommend if: <$70,000 per life year Do not recommend if: >$100,000 per life year	Recommend if: <$30,000 per life year Do not recommend if: >$70,000 per life year
Weak	Recommend if: <$30,000 per life year Do not recommend if: >$70,000 per life year	Recommend if: <$30,000 per life year Do not recommend if: >$30,000 per life year

was based on search findings from Medline, Econlit, Health Star, and the National Health Service Economic Evaluation Database. Some leading edge effectiveness studies published in 2000 and 2001 were also obtained given that recent cost-effectiveness studies may not have included such medical findings. The process identified over 90 journal articles. The AMI cost-effectiveness studies were screened within the topics of diagnostic strategies, angioplasty, drug therapy, cardiac rehabilitation and secondary prevention. Costing studies for AMI and coronary heart disease were also considered.

The results of the key cost-effectiveness findings are discussed below, along with the recommendations published in the 1999 guidelines. The implications of the cost-effectiveness studies for any new reviews of the 1999 guidelines in both the international and Australian context are discussed. The methodology adopted is consistent with guidelines by NHMRC [40] with the key features outlined below.

Levels of evidence criteria and grades of recommendation

Firstly, key international cost-effectiveness findings were extrapolated into the Australian setting by applying the health PPP index published by the OECD [43]. We also applied NHMRC [40] criteria for identifying grades of recommendation for the adoption of preferred technology involving combinations of relative effectiveness versus relative costs and the choice of cost-effectiveness cut-off points for Australia (Table 1). Only cost-effectiveness studies could be evaluated using the NHMRC cut-off points. Levels of evidence criteria were applied rating economic evaluation on the methodological rigor in estimating clinical effectiveness and costs. This is based on Drummond et al. [15] checklist.

We applied criteria for the critical appraisal (internal validity) of a cost-effectiveness publication by Drummond et al. [15], using a scoring system that we developed relating to the ten-point checklist. We separately scored the effectiveness and costing methodology of each paper using this checklist. The Drummond et al. checklist questions 4–9 were scored separately for costs and consequences; 'yes' was scored as 1 and 'no' as 0. Questions 1, 2, 3 and 10 accrued scores for consequences only. A total score achievable for each published paper reviewed was 6 for costs and 10 for consequences. Hence we achieved a higher focus and 'weight' on questions 4–9 in discerning the rigor of costing methodology. A score of 4 (or higher) out of 6 for costs was deemed to be 'strong' on methodological rigor. Scoring under 4 for costs was defined as weak. A score of 6 (or higher) out of 10 for consequences was deemed to be strong; under 6 being deemed 'weak'.

Supplementary criteria was also applied to help score the methodological rigor of the consequences in each study for the Drummond et al. [15] questions 1, 3 and 6 [39]. This related to quality criteria for randomised controlled trials, cohort studies, case control studies and systematic reviews. We also ranked the effectiveness component of each study according to NHMRC level of evidence (levels I–IV) ranging from randomised trials at level 1 through to evidence from case series, either post-test or pre-test/post-test at level 4. These additional sources of information were supplementary to Drummond et al. [15] critical appraisal checklist, and enhanced its application in the study. We determined that where a study was graded as NHMRC level of evidence IV for effectiveness, the study would be overall graded as weak on consequences even if a score of 6 or higher out of 10 had been achieved from the Drummond et al. [15] checklist. The evidence checklist describing strength of evidence, size of effect and relevance of evidence in NHMRC [39] was also considered when grading papers. Scoring was undertaken by two members of the CPWG with expertise in health economics who reached consensus on the scores for each question through extensive discussion of each paper. The Drummond et al. [15] checklist combined with the NHMRC level of evidence for effectiveness studies provided an outstanding basis and discipline for the critical evaluation of each cost-effectiveness paper. Importantly, we also used the results from the UK Website for the National Health Service Economic Evaluation Database to assist with our initial review of the papers.

Our scoring system assessed costing and effectiveness methodology and strength of evidence used in each paper were graded as either weak or strong. This then enabled us to apply the NHMRC [40] matrix for 'assessing evidence using shadow prices' and determine recommended threshold cut-off points for shadow prices as outlined in Table 1.

NHMRC [40] indicates that interventions might require further consideration if they fall in the ranges of $70,000–$100,000 per life year saved and rank highly for evidence on costs and effects, or if they are in the range $30,000–$70,000 per life year saved and rank highly on one but not the other. Factors identified by NHMRC [40] that might make an intervention more attractive and considered particularly relevant to the AMI papers reviewed were: quality of life, survival improved, functional status, condition is severe and preventable, prevents adverse flow-on effects into other sectors and equity implications.

Economic evaluation of treatment interventions for AMI

Percutaneous transluminal coronary angioplasty

Primary PTCA versus thrombolysis (tissue plasminogen activator)

In order to improve prognosis of AMI it is crucial to achieve early optimal reperfusion of myocardial tissue. In-hospital and late mortality of AMI have been significantly reduced using thrombolytic agents. Over the past decade, transcatheter therapeutic interventions became feasible for elective coronary interventions and for acute coronary syndromes [28]. However, there has been no consensus about whether primary percutaneous transluminal coronary angioplasty (PTCA) has a cost-effective advantage over thrombolysis in AMI. Mullen et al. [35] compared the cost-effectiveness of primary PTCA to thrombolytic treatment with tissue plasminogen activator (tPA) for AMI management using data from published prospective randomised studies. The treatment strategies involved either intravenous administration of 100 mg tPA according to a front-loaded dosing regimen or urgent coronary angiography and, if feasible, consecutive primary PTCA. If signs of coronary ischaemia occur within the hospital stay, the patient is to undergo re-angiography and, if applicable, a re-PTCA.

A cost-effectiveness analysis estimated the therapy costs by applying the reimbursement paid by Austrian public health insurance organisations including facilities, instruments, staff and drugs. Coronary intervention rates and re-intervention rates were extracted from published studies. Assuming a moderately reduced in-hospital mortality for patients treated with primary PTCA (4.8%) compared to tPA (6.6%) on the basis of AMI in a 60-year-old man, the estimated additional cost per life saved was 274 European currency units (ecu; Australian $ 308). Cost per life saved was sensitive to the range of intervention and re-intervention rates. Assuming a moderate in-hospital survival benefit from primary PTCA in patients with AMI, PTCA is cost-effective compared to tPA. These findings and the methodological rigor used in the study were rated as strong on both costs and effectiveness using the NHMRC matrix and Drummond et al. [15] checklist. The results easily fall within the NHMRC threshold to recommend if less than $70,000 per life year saved.

A limitation of the study was that analyses were based on reimbursement and not actual costs. However, the authors argue that according to expert opinion the actual costs for the interventions or for thrombolyic treatment appear to be comparable to the amount of reimbursement, at least for an uncomplicated intervention, which was assumed for the base case. Another limitation is the very small number of prospective, randomised studies leading to a wide range of intervention and outcome probabilities [35].

These findings do not conflict with the USA guidelines, which state that Gibbons et al. [18] found that those who underwent primary PTCA were less likely to require coronary revascularisation for recurrent ischaemia over a 6-month follow-up period than those treated with alteplase (tPA).

Low-risk AMI: early discharge after angioplasty

Primary PTCA is a safe and effective method of providing reperfusion therapy for AMI, and when compared to thrombolysis, it reduces risk of recurrent ischaemia, reinfarction, death and stroke (for review see [23]). A key issue is whether acute catheterisation data can be used to risk stratify patients after primary PTCA, and whether accelerated hospital treatment is cost-effective in low-risk patients. In low-risk MI patients only a few studies have investigated the need for intensive care and non-invasive testing or the appropriate length of hospital stay.

The second Primary Angioplasty in Myocardial Infarction (PAMI-II) study [23] therefore evaluated whether primary PTCA, with discharge 3 days later, is cost-effective in low-risk patients. AMI patients had emergency catheterisation with primary PTCA when appropriate. Low-risk patients were defined as aged under 70 years and having left ventricular ejection fraction greater than 45%, one- or two-vessel disease, successful PTCA and no persistent arrhythmias. These low-risk patients were randomised to receive accelerated care [admission to a non-intensive care unit and day 3 hospital discharge without non-invasive testing (n=237)] or traditional care (n=234). Patients with accelerated care had similar in-hospital outcomes but were discharged 3 days earlier (4.2 vs. 7.1, P=0.0001) and had significantly lower hospital costs (US$ 9,658 vs. US$ 11,604, A$ 9,465 vs. A$ 11,372; P=0.002) than those with traditional care. At 6 months accelerated and traditional care groups had similar rates of mortality, unstable ischaemia, reinfarction, stroke, congestive heart failure or their combined occurrence. Early identification of low-risk patients with AMI allowed safe omission of the intensive care phase and non-invasive testing, and day 3 hospital discharge strategy, resulting in substantial cost savings. This accelerated care approach may reduce health costs by $293 million annually in the USA [23].

The USA guidelines cover primary PTCA but not in the context of risk stratification. The cost-effectiveness results in the study by Grines et al. [23] indicate that where PTCA is used to identify high and low risk, accelerated care for low-risk patients is appropriate. These findings do not disagree with the USA guidelines but provide additional information about risk stratification that is of great value. A review of the USA guidelines should include reference to this study and include details of the treatment protocol in PAMI-II, patient eligibility and definitions of accelerated care.

Cost advantages of an ad hoc angioplasty

PTCA performed during the same sitting as diagnostic coronary angiography, called 'ad hoc' PTCA has generated much controversy, particularly concerning its safety [49]. The underlying assumption of pursuing an ad hoc strategy is that a more rapid and definitive resolution of the ischaemic coronary problem will yield significant cost savings through lower length of stay and improved patient convenience [27]. Adele et al. [1] analysed the cost advantage of 'same-sitting diagnostic catheterisation and PTCA' (ad hoc) compared to 'staged PTCA'. 395 patients had PTCA over 6 months. The only previous study that examined the cost advantage of ad hoc PTCA had been undertaken much earlier by O'Keefe et al. [44].

Adele et al. [1] examined costs on three clinical situations based on indications for PTCA, including stable angina, unstable angina and post-MI. To enable meaningful comparisons between staged and ad hoc procedures they stratified patients according to indication for PTCA. They excluded patients who had primary PTCA for AMI as these procedures were by definition uniformly ad hoc. No comparable staged procedures exist. These groups have high costs and their inclusion would unfairly bias the results against ad hoc group. There was no significant cost advantage of an ad hoc approach within any of the strata, although there was a non-significant cost advantage trend toward an ad hoc approach for stable angina. For patients treated with conventional balloon PTCA alone, the lack of a significant difference between ad hoc and staged strategies persisted. For patients who received stents there was a significant cost advantage of an ad hoc approach in all three clinical strata. Complications were important cost drivers. Significant cost differences detected for stent cases were $1,338 (A$ 1,151) for stable angina, $1,669 (A$ 1,435) for unstable angina and $2,782 (A$ 2,393) for post-MI patients. Cost savings with an ad hoc strategy of PTCA could not be consistently demonstrated. The cost advantage of an ad hoc approach may occur where the risks are low (e.g. stable angina) or where devices such as stenting carry reduced risk of complications. A small increase in the complication rate negates any financial advantage of an ad hoc approach [1].

Because stenting is effective in addressing dissections and is associated with falling complication rates, it may be safe and cost-saving to perform ad hoc PTCA in patients with coronary lesions of a morphology and calibre suitable for stenting. It would be of interest to examine whether the size of the coronary arteries differed among the ad hoc and staged PTCA and stent groups. However, Adele et al. [1] did not collect such data prospectively. Similarly, the use of GP IIb-IIIa blockers reduces risk of PTCA-related complications. Abciximab was used at the discretion of the operator during the study. However, Adele et al. [1] did not systematically track drugs used in the catheterisation laboratory and cannot conclude whether abciximab can contribute to a safe or cost-effective ad hoc strategy [1]. The author's focus was on complications and not composite events nor any events such as AMI, death or stroke. Further, there was limited information provided about the nature of the complications investigated. The USA guidelines do not specifically comment about staged versus ad hoc PTCA. The literature review of the guidelines could include reference to this study, noting that the cost advantage of ad hoc angioplasty may be most readily realised in the case of low risk (stable angina) or where the devise (such as a stent) has less complications associated with its use.

GPIIb/IIIa antagonist drugs

Tirofiban after AMI and/or high-risk angioplasty

Coronary angioplasty outcome has improved over the past decade. However, acute closure remains a significant risk occurring in 4–13% of patients [53] and is associated with increased risk of MI, emergent coronary surgery and death [59]. Efforts to reduce acute closure have been aimed mainly at mechanical and drug interventions to prevent thrombosis. GPIIb/IIIa receptor is important on the platelet for fibrinogen cross-linking and platelet aggregation. These drugs are new and prevent complications after high-risk angioplasty.

Weintraub et al. [60] assessed the impact of a GPIIb/IIIa blockade drug called tirofiban on costs during initial hospitalisation and at 30 days among high-risk coronary angioplasty patients. The RESTORE trial [48] was a multinational, blinded placebo-controlled study of 2,197 patients with AMI or unstable angina undergoing angioplasty who were randomised to tirofiban or placebo. The economic study was a prospective substudy of the RESTORE trial including 1,920 USA patients. Costs were based on health care utilisation and costs measured directly in 820 USA patients at 30 sites. They found a 36% difference in composite event rates of death, MI and revascularisation at 2 days between tirofiban and placebo (8% vs. 12%, *P*=0.002). This resulted from a reduction in non-fatal MI, repeat angioplasty, coronary surgery and stent placement. These clinical benefits were similar at 30 days, with a 16% reduction in composite event (*P*=0.10). In-hospital cost, including professional and study drug costs, was US$ 12,145 (A$ 11,902) with placebo, versus US$ 12,230 (A$ 11,985) with tirofiban (*P*=0.75). The 30-day cost was US$ 12,402 (A$ 12,154) with placebo, versus US$ 12,446 (A$ 12,197) with tirofiban (*P*=0.87). Tirofibin decreased in-hospital and 30-day events after high-risk angioplasty. Beneficial clinical effects of tirofiban in high-risk patients can be achieved with no increased cost.

More data are needed to assess the cost-effectiveness of GPIIb/IIIa blockade in lower risk subgroups. To date, studies utilised a bolus or loading infusion followed by a maintenance intravenous infusion. Oral or transdermal GPIIb/IIIa blockers or other antiplatelet agents may extend and improve the utility of IV GPIIb/IIIa blockade for unstable angina and high-risk angioplasty. Further, oral platelet blockade may extend the use of these agents into other patient categories. Establishing the cost-effectiveness of these agents will be important [60]. The USA guidelines do not address the cost-effectiveness associated with use of tirofiban in unstable angina, AMI and/or high-risk angioplasty for AMI. Rather, they refer to effectiveness in non-ST elevation. Any revisions to the USA guidelines should include reference to the study by Weintraub et al. [60].

Tirofiban

A Swiss study by Szucs et al. [56] analysed whether use of tirofiban plus heparin and aspirin saves direct health costs, compared with heparin and aspirin alone in patients with acute coronary ischaemic syndrome. The results of the randomised double-blind controlled clinical trial called the PRISM PLUS study formed the basis [47]. The hypothetical cohort comprised 100 patients with unstable angina and/or non-Q-wave MI. An incremental cost-consequence analysis was undertaken from the hospital perspective for the first 7 days. Costs for managing refractory ischaemic conditions and MI were analysed, including incremental days on wards, intensive care unit and also revascularisation procedures. Drug costs were based on a loading dose of 0.4 μg/kg per minute and a maintenance dose of 0.1 μg/kg per minute for tirofiban at a

cost of 166.50 ecu per vial. A loading dose of heparin was 5000 U, with a maintenance dose of 1000 U/h. The costs of managing ischaemic complications were based on typical practice patterns in Swiss hospitals. Incremental drug costs per 100 patients were 49,954 ecu (A$ 47,598). The additional use of tirofiban resulted in net savings of 33,418 ecu (A$ 31,841) per 100 patients, through lower costs of treating refractory ischaemic conditions (lower by 48,275 ecu, A$ 45,997) and MI (lower by 35,097 ecu, A$ 33,442). Tirofiban is cost-saving in acute coronary ischaemic syndromes and improves the efficiency of managing these patients during the initial hospitalisation. The primary efficacy variable was defined as a composite endpoint of death, MI and refractory condition 7 days after randomisation.

However, there are three limitations of the study. Firstly, the cost structure was mainly determined by expert opinion from physician interviews. Secondly, incremental costs only relate to the first 7 days after treatment. Additional costs may become evident later, although offsetting these are the likely lower costs from fewer repeat revascularisations. Therefore a longer term study would be useful [56]. Finally, the original PRISM study had another arm (tirofiban+placebo+aspirin) [46]. However, this had to be abandoned in the trial due to safety reasons. This arm is not mentioned in the study by Szucs et al. [56] but is important.

The above study involves the administration of tirofiban to non-Q-wave MI patients during initial hospitalisations. The USA guidelines refer to the PRISM and PRISM PLUS studies. However, the cost-effectiveness study by Szucs et al. [56] is not cited. Any revisions to the guidelines could refer to the cost-effectiveness study highlighting that during initial hospitalisation, tirofiban and heparin and aspirin is cost-effective for non-Q-wave MI and unstable angina. The following protocol, based on the PRISM and Szucs et al. [56] studies is cost-effective: loading doses of 0.4 µg/kg per minute and a maintenance dose of 0.1 µg/kg per minute for tirofiban. Heparin is administered with a loading dose of 5000 U and a maintenance dose of 1000 U per hour. Treatment course involves three vials for an infusion period of 3 days. Aspirin (325 mg) is also administered in early stages. The drug combination of tirofiban+placebo+aspirin is contraindicated, based on the findings of the PRISM study.

Abciximab

Few question the superior efficacy of abciximab (ReoPro) compared with conventional high-dose heparin therapy during percutaneous intervention given the results of the trials data from the Evaluation of 7E3 for the Prevention of Ischaemic Complications (EPIC), c7E3 Fab Antiplatelet Therapy in Refractory Angina (CAPTURE), and Evaluation in PTCA to Improve Long-Term Outcome with Abciximab GP IIb/IIIa Blockade (EPILOG) [21]. Economic analyses indicate that the incremental direct medical care cost of abciximab is US$ 290–$600 (A$ 299–A$ 618) per patient treated in EPIC and EPILOG populations. For AMI and unstable angina patients abciximab produces cost savings at 6 months. Given abciximab's significant incremental effectiveness, its relatively small incremental cost yielded a highly cost-effective therapy in the EPIC and EPILOG patient populations [21].

EPIC trial patients (n=2099) were randomised between November 1991 and November 1992 at 56 institutions in the USA. Patients referred for coronary angioplasty at each site were eligible if at high-risk for ischaemic complications. Patients included those with AMI within 12 h of symptom onset, early post-infarction angina or unstable rest angina, or high-risk angiographic lesion morphology as defined by AHA/ACC criteria. Exclusions included those aged 80 years or older and those at high risk of bleeding. In the EPIC protocol all patients received 325 mg aspirin orally before angioplasty and once a day thereafter. They also received intravenous heparin before angioplasty and for at least 12 h after the procedure. Patients were randomised into three treatment groups in a double-blind design, involving: (a) bolus and infusion c7E3 Fab (abciximab), (b) bolus c7E3 Fab (abciximab) and placebo infusion, and (c) placebo bolus and placebo infusion [32]

After 6 months 73.8% of patients treated with abciximab in EPIC were alive and free of MI and repeat revascularisation, compared with 64.9% of the placebo group. Incremental effectiveness is a reduction in the rate of these outcomes by 8.9 events per 100 patients treated. Incremental cost of treating 100 patients in the EPIC trial was US$ 29,000 (US$ 290×100; A$ 29,870). The incremental cost of abciximab per event prevented is US$ 3,258 (A$ 3,356). Events were defined as AMI, deaths and repeat procedures. This incremental cost-effectiveness is equivalent or superior to other widely accepted therapies eg the incremental cost of stenting per event prevented is $29,590 or $23,600 per quality-adjusted life year (QALY) gained [21]. The USA guidelines make no reference to these findings. Any review of the guidelines should discuss these findings. In applying the NHMRC grades of recommendation criteria and the Drummond et al. [15] checklist, we rated the study as high on both cost and effectiveness. The incremental cost per event prevented of US$ 3,258 (A$ 3,356) seems very cost-effective.

Mark et al. [34] also discuss the EPIC trial, noting that acute administration of GPIIb/IIIa is beneficial but expensive. Mean hospital costs in EPIC trial, exclusive of drug costs, were equal for placebo, abciximab bolus, and abciximab bolus+infusion, at approximately US$ 13,400 (A$ 13,802). Breakdown of these costs demonstrated that the decrease in ischaemic complications (approximately $600 per patient) in the treatment arms was offset by higher costs required to treat bleeding complications. In contrast, 6 months after discharge 23% fewer hospitalisations, 22% fewer revascularisation procedures, with mean cost savings of US$ 1,270 (A$ 1,308) per patient treated. With a cost of US$ 1,407 (A$ 1,449) for the abciximab bolus and infusing regime, the incremental 6 month cost for this treatment averaged US$ 293 (A$ 302) per patient. Agent recouped almost all initial therapy costs with significant benefits [32, 34].

Thrombolytic therapy

Recombinant tissue plasminogen activator versus streptokinase

The Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Artery (GUSTO) trial has demonstrated that tPA when infused in an accelerated form (with intravenous heparin), is more effective than

two streptokinase regimes [24]. The GUSTO study investigated four different treatment strategies, including: (a) streptokinase plus subcutaneous heparin, (b) streptokinase plus intravenous heparin, (c) tPA given over 90 min (accelerated tPA) plus intravenous heparin, and (d) streptokinase and tPA plus intravenous heparin.

Despite the much higher cost of tPA than streptokinase, economic evaluation of the GUSTO trial found that tPA is more cost-effective than streptokinase for treating AMI [31]. Sub-group analysis of the GUSTO results indicates that tPA is a significant advantage in patients aged under 75 years and in those with anterior AMI. Such an advantage is not found in older patients and in those with a non-anterior AMI [24]. The economic analysis by Mark et al. [31] also includes a sub-group analysis, but evaluation of different strategies with a sub-group selective use of streptokinase and tPA was not undertaken.

Lorenzoni et al. [30] therefore undertook a cost-effectiveness analysis of the differences in thrombolytic costs across countries and efficacy differences across patient sub-groups. They analysed the costs of streptokinase and tPA in Germany, Italy, UK, and USA, and the 30-day mortality found in the GUSTO trial. Incremental costs were calculated for each life saved when streptokinase is substituted by tPA. Incremental costs were calculated for each life saved for two protocols, implying a selective use of streptokinase and tPA. The *age-selective protocol* involved tPA in patients aged 75 years or younger, and streptokinase in older patients. The *site-selective protocol* involved tPA in anterior AMI, and streptokinase in non-anterior AMI. The incremental costs for each life saved when streptokinase is substituted by recombinant tPA in all GUSTO patients vary greatly between countries.

The incremental cost of each life saved based on treating 1000 patients with streptokinase substituted for tPA in GUSTO patients varied. The amounts were 132,199 ecu (A$ 154,591) in Germany, 146,652 ecu (A$ 227,792) in Italy, 100,757 ecu (A$ 140,496) in the UK and 198,254 ecu (A$ 190,106) in the USA. Anterior AMI costs per additional life saved were 69,758 ecu (A$ 81,363) in Germany, 77,185 ecu (A$ 119,890) in Italy, 53,030 ecu (A$ 73,945) in the UK and 104,344 ecu (A$ 100,055) in the USA.

The incremental costs for each life saved are 31%, 45%, and 97% higher in Germany, Italy, and USA than in the UK. The cost-efficacy of recombinant tPA vs. streptokinase in AMI varies greatly between countries due to differences in drug costs. Use of a site-selective protocol implies a halved cost-effectiveness ratio compared to the use of recombinant tPA in all cases of AMI. Use in anterior AMI is particularly cost-effective as it halves the costs for each life saved. The cost-effectiveness ratio of age-selected protocol is very similar to the exclusive use of tPA. Therefore patient selection based on age is inappropriate [30].

In applying the NHMRC grades of recommendation criteria and the Drummond et al. [15] checklist we noted that the results were expressed in costs per life saved, rather than per life year saved. Further work to determine costs per life year saved would be desirable. The study was rated as weak on costing methodology and strong on effectiveness methodology. The costing methodology and its relationship to sub-groups was unclear.

The USA guidelines note that it has been well established that thrombolytic therapy provides survival benefit for patients with AMI based on several key trials including, among others, alteplase, another name for tPA. However, the guidelines make no reference to Lorenzoni et al. [30]. That study and also that of Mark et al. [31] found that the use of tPA is particularly cost-effective relative to streptokinase.

Anticogulants

Enoxaparin versus unfractionated heparin

Standard care for hospitalised patients with unstable angina includes aspirin and infusion of unfractionated heparin. Low molecular weight heparin (LMWH) has recently been proposed as an antithrombotic therapy potentially superior to unfractionated heparin [58]. In the Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q Wave Coronary Events (unstable angina or non-Q-wave MI; ESSENCE) trial, subcutaneous LMWH (enoxaparin) reduced 30-day incidence of death, MI and recurrent angina relative to intravenous unfractionated heparin in 3171 patients with unstable angina or non-Q-wave MI from 23.3% with unfractionated heparin to 19.8% with enoxaparin. There was no increase in major bleeding. Mark et al. [33] undertook an economic assessment of enoxaparin versus unfractionated heparin. Of the 936 ESSENCE patients in the USA, 655 had hospital billing data. Multivariate linear regression calculated hospital costs for the remainder. The Medicare fee schedule was used to calculate the physician fees. During initial hospitalisation, utilization patterns were reduced for the enoxaparin group, especially for coronary angioplasty (15% versus 20% for heparin). At 30 days the largest reductions were for diagnostic catheterisation and coronary angioplasty. The mean cost of a course of enoxaparin in the USA was $155, compared to $80 for heparin (i.e. $75 incremental costs of administering enoxaparin rather than heparin). Total medical costs (hospital, physician, drug) for the initial hospitalisation were US$ 11,857 (A$ 10,197) for Enoxaparin and US$ 12,620 (A$ 10,853) for heparin, a cost advantage for Enoxaparin US$763 (A$ 656) at hospital discharge. By 30 days, cost savings for enoxaparin was US$ 1,172 (A$ 1,008). In 200 bootstrap samples of the 30 day data, 94% of the samples showed a cost advantage for enoxaparin. In patients with acute coronary syndrome LMWH (enoxaparin) improves clinical outcomes and has cost savings relative to unfractionated heparin. The study did not include out-patient care, nor the productivity costs related to loss of employment. The limited 30 day follow-up leaves open the question of whether the observed clinical and economic benefits would be preserved over a longer time frame [33]. This issue is addressed in the following study.

One-year follow-up data from the ESSENCE trial found that LWMH (enoxaparin) compared with unfractionated heparin in patients hospitalised with unstable angina or non-Q-wave MI has a 10% reduction in the cumulative 1-year risk of death, MI or recurrent angina [22]. Cumulative 1-year data from Canadian centres comprising 1259 ESSENCE patients (40% of the total ESSENCE sample) was analysed by O'Brien et al. [42]. Patient specific data from initial hospital stay cumulative to 1 year were available for utilisation of drugs, diagnostic cardiac catheterisa-

tion, PTCA, CAGS and hospital days. Hospital resources were costed using data from one Ontario hospital. During the initial hospitalisation enoxaparin had reduced diagnostic catheterisation, and revascularisation procedures, with the largest effect occurring for PTCA (15% versus 10.6%, *P*=0.03). After 12 months lower risk and revascularisation costs more than offset increased drug costs for enoxaparin, with per patient cost savings of Canadian $1,485 (A$ 1,708; *P*=0.06). Sensitivity analysis with lower hospital daily costs predicts cost savings of Canadian $1,075 (A$ 1,236) per patient over 12 months. The acquisition and administration cost of enoxaparin is higher than for unfractionated heparin ($101 vs. $39), but in patients with acute coronary syndrome the reduced need for hospitalisation and revasculation over 1 year more than offsets this initial difference in costs. This evidence indicates that enoxaparin is less costly and more effective than unfractionated heparin in this indication. A limitation of the study is their use of a simple cost-prediction model with regressions to estimate the total cost per patient as a function of hospital stays and procedures from a secondary hospital cost data base [42].

No changes are suggested for the current USA guideline recommendation for unfractionated heparin. However, the conclusion in the USA guidelines regarding LMWH (enoxaparin) for non-Q-wave MI does require attention along with the literature review which only covers the 30-day follow-up for both effectiveness and cost-effectiveness studies of the drug. The USA guidelines indicate that ESSENCE reported a 16% reduction in the 14-day incidence of death, MI or recurrent angina with enoxaparin to unfractionated heparin [13]. The enoxaparin group continued to have fewer events than the unfractionated heparin group through to 30 days, when a primary end-point had occurred in 19.8% of the enoxaparin group and 23.3% of the unfractionated heparin group (*P*=0.016). Patients treated with enoxaparin were also significantly less likely to require revascularisation procedures within 30 days (27% versus 32.2% *P*=0.001). However, the guidelines have not cited nor discussed the 1 year follow-up study of ESSENCE by Goodman et al. [22], which found that enoxaparin was associated with a 10% reduction in the cumulative 1-year risk of death, MI or recurrent angina. The related cost-effectiveness study by O'Brien et al. [42] found that enoxaparin (LMWH) is less costly, with per patient savings of Canadian $1,485 over 12 months, and more effective than unfractionated heparin for patients with non-Q-wave MI or unstable angina. The cost-effectiveness study was published after the guidelines and could be included in future guideline reviews.

Antiarrhythmics

Amiodarone in post-infarction patients and diagnostic strategies (non-invasive, invasive and electrophysiological testing)

The prevention of malignant ventricular tachyarrhythmias is a key problem after AMI. β-Adenergic blocking agents are effective in reducing incidence of sudden death after MI [61]. Complementary therapeutic approaches have been investigated. Amiodarone has not reduced total or cardiac mortality although it has reduced arrhythmic mortality. These findings do not support a systematic prophylactic use of amiodarone in post-infarction patients but suggest a role for it in patients at high risk of arrhythmias [11, 26].

However, the cost-effectiveness of amiodarone therapy in post-infarction patients is still unknown, and no study has determined which diagnostic strategy should be used to maximise amiodarone survival benefit while improving cost-effectiveness. With regard to risk assessment, depressed heart rate variability is associated with cardiac mortality, especially sudden death. However, programmed ventricular stimulation in patients preselected by non-invasive techniques has an additional benefit of improving diagnostic accuracy. Therefore the combined use of programmed ventricular stimulation and heart rate variability analysis might be more cost-effective than a simple non-invasive approach.

Pedretti et al. [45] therefore evaluated two related key issues. Firstly, the cost-effectiveness of amiodarone therapy in post-infarction patients. Secondly, the influence of alternative diagnostic strategies (non-invasive only vs. non-invasive and electrophysiological testing) on survival benefit and cost-effectiveness ratio of amiodarone therapy. The non-invasive strategy involved heart rate variability assessment.

Heart rate variability analysis on 24-h Holter monitoring was used as a screening test for amiodarone after MI. Base case analysis evaluated survivors of recent MI free from contraindications to amiodarone, of whom 54% and 40% were treated with thrombolysis and β-blockers, respectively. Three groups were considered: (a) patients receiving no amiodarone therapy; (b) all patients with depressed heart rate variability treated with amiodarone during the first 2 years after MI, after receipt of an oral loading dose during an additional week in the hospital and undergoing baseline tests to screen for potential drug toxicity during follow-up, and (c) all patients with depressed heart rate variability undergoing programmed ventricular stimulation, and only those with positive programmed stimulation, defined as the induction of sustained monomorphic ventricular tachycardia of less than 270 beats/min, received amiodarone therapy.

Variable costs and quality-adjusted life expectancy over 20 years were predicted using a Markov simulation model. Costs and charges were calculated using an Italian and USA hospital. Amiodarone therapy for patients with depressed heart rate variability and a positive programmed ventricular stimulation was dominated by a blend of the two alternatives. Compared with the no-treatment strategy, the incremental cost-effectiveness ratio of amiodarone therapy in patients with depressed heart rate variability per QALY was US$ 10,633 (A$ 10,739) in Italy and US$ 39,422 (A$ 39,816) in the USA using Italian costs and American charges, respectively. Compared with a non-interventional option, Amiodarone in patients with depressed heart rate variability is a more appropriate approach than the alternative based on the combined use of heart rate variability and electrophysiological study [45]. The study was graded as strong on both costing and effectiveness evidence applying the NHMRC grades of recommendation with the Drummond et al. [15] checklist. The findings easily fall within the threshold to recommend if less than $70,000 per life year saved. However, heart rate variability analysis is not usual practice at the present time.

The USA guidelines do recommend use of amiodarone in ventricular tachycardia/ventricular fibrillation in the context of sustained monomorphic ventricular tachycardia not associated with angina, pulmonary enema, or hypotension (blood pressure less than 90 mmHg). In this context, the US guidelines indicate that the patient should be treated with one of four alternatives, which include amiodarone at the dose of 150 mg infused over 10 min followed by constant infusion of 1.0 mg/min for 6 h and then a maintenance infusion of 0.5 mg/min.

The USA guidelines also make separate reference to routine testing – assessment of ventricular arrhythmia via ambulatory Holter monitoring in preparation for discharge. Pedretti et al. [45] have determined that a cost-effective form of treatment involves the application of 'amiodarone for depressed heart rate variability'. This involved the assessment of the heart variability by the Holter screening assessment for amiodarone after MI, and in whom 54% and 40% were treated with thrombolysis and β-blockers, respectively.

However, the USA guidelines include various caveats regarding the use of one or more non-invasive tests which might be recommended for routine clinical practice in identifying increased likelihood of arrhythmic events. They emphasise that the positive predictive value is unacceptably low (<30%). Further, they state that the whilst positive predictive value of such tests can be modestly improved by combining several test results, the therapeutic implications of positive findings are unclear:

Insufficient data are available to indicate whether general therapies such as B-adrenoceptor blockade, ACE inhibition, and revascularization procedures or specific interventions such as treatment with amiodarone or implanatable cardioverter-defibrillator, targeted for high risk patients identified by a combination of noninvasive tests after MI can more favorably impact mortality [19]. Moreover, it is difficult to justify the costs of the routine use of these procedures in the absence of therapeutic guidelines or demonstrated clinical benefits associated with a positive test. Until these issues are resolved, use of these tests cannot be recommended in routine management, although they will continue to be of interest as investigational tools for specific risk assessment protocols [51].

Any revisions to the USA guidelines could include reference to the study by Pedretti et al. [45] and its key findings as it has been clearly demonstrated that a cost-effective approach is the use of amiodarone for depressed heart rate variability, as measured by the non-invasive diagnostic procedure, the Holter. However, clinical practice changes would not be recommended on the basis of one single study. Further, the use of the Holter requires careful analysis and there would be issues of costs for its adoption in Australia. It is currently not readily available world wide. Equipment and operating costs require careful attention.

Serum markers

Cardiac troponin 1 in chest protocol

The troponins are rapidly becoming the new standards of cardiac testing to facilitate diagnosis of myocardial injury in early decision making in addition to creatine kinase MB (CK–MB) and myoglobin. Anderson et al. [8] assessed the effect of adding an automated cardiac troponin I (c-TnI) assay to a cardiac panel comprising CK-MB, myoglobin, total CK activity and a calculated CK-MB relative index. Samples were collected on admission and at 3, 6 and 8 h after admission. Data were also collected on a control group, with change implemented through c-TnI testing and the effect of the change was measured on the experimental group having otherwise equivalent diagnostic and therapeutic pathways. They assessed differences in patient hospital and cardiac care, length of stay, time to cardiac catheterisation and laboratory and hospital charges and costs. Adding c-TnI to the testing regime significantly decreased length of stay from 3.7 days in the control group to 3.2 days in the test group (P=0.02). None of the other measures differed significantly.

Total hospital costs had a non-significant decrease of $400 per patient in the test group compared to the control. The sub-group of non-Q-wave AMI and unstable angina had a non-significant increase in such costs, offset by the large number of low-risk patients in whom total and variable costs declined by one-third. Overall, those classified as low risk for acute MI had significantly shorter length of stay and significantly lower total and variable hospital costs. Average costs for low-risk patients declined from US$ 6,170 (A$ 5,306) to US$ 4,550 (A$ 3,913; P=0.003). These data suggest that adding c-TnI as a cardiac marker is an effective tool to rule out an acute cardiac event and allow a 1-day earlier discharge of this large low-risk group, which accounts for about 40% of admitted chest pain patients.

Laboratory costs increased slightly in the test group by $50 per patient over the control group. However, the sub-group of non-Q-wave AMI patients' laboratory costs declined by an average of $80. Low-risk patients stayed even, and the unstable angina patients had an increase (but nonsignificant) in laboratory costs by $120 per patient. Anderson et al. [8] conclude that c-TnI testing appropriately used in standardised protocols is effective in providing improved diagnosis of patients with chest pain and can reduce associated costs. In particular, low-risk patients lose less time away from work and home and are charged less to rule out acute cardiac disease. Adding automated c-TnI assay to a cardiac panel of CK-MB, myoglobin, total CK activity, and calculated CK-MB relative index decreased length of stay relative to control group. Low-risk MI patients had shorter length of stay and lower costs. For unstable angina, patients had non-significant increase in laboratory costs [8]. Anderson et al. [8] cite the WHO guidelines for diagnosis of AMI; at least two of the following three indicators must be present: (a) Serial electrocardiography ST segment elevation of at least 1 mm in at least two contiguous leads, (b) history of chest pain of more than 20 min duration or typical current symptoms and (c) serial rise in a biochemical serum marker of myocardial necrosis [20]. These guidelines highlight the importance that a cardiac-specific marker of myocardial damage could have in the diagnostic process.

The USA guidelines make no reference to the study by Anderson et al. [8]. However, they do cite various earlier studies that indicate that CK-MB lacks sufficient sensitivity and specificity, highlighting the need for more sensitive and cardiac specific markers of myocar-

dial necrosis. Numerous investigations have reported elevated levels of cTnI or cTnT, providing additional prognostic information. CK-MB isoforms are another new serum marker. The Diagnostic Marker Cooperative Study investigators [62] analysed the diagnostic sensitivity and specificity for MI of total CK-MB, CK-MB subforms, myoglobin, cTnI and cTnT. They found CK-MB subforms the most-efficient for early diagnosis (within 6 h) of MI, whereas cTnI and cTnT were highly cardiac specific and especially efficient for later diagnosis of MI. The conclusions of these investigators, cited in the USA guidelines, are broadly in agreement with the above cost-effectiveness findings. The researchers concluded that either a single assay (CK-MB subforms) or a select combination (CK-MB subform and a cardiac specific troponin) reliably triages patients with chest pain and could possibly lead to improved therapy and reduced costs of care of acute cardiac syndrome patients. However, the economic study by Anderson et al. [8] provides additional insights on utilisation and costs: adding c-TnI can effectively rule out an acute cardiac event and allow for a 1-day earlier discharge accounting for 40% of admitted chest pain patients. Overall, those classified as low risk for AMI had significantly shorter length of stay and significantly lower total variable costs. The full list of tests used were CK-MB, myoglobin, total CK activity and calculated CK-MB relative index.

Secondary prevention

Antioxidants: vitamin E

Epidemiological studies suggest that vitamin E (α-tocopherol) plays a preventive role in reducing the incidence of atherosclerosis. The Cambridge Heart Antioxidant Study (CHAOS) randomised 2,002 patients with angiographically confirmed atherosclerosis to supplementation with α-tocopherol, at a dose of either 400 or 800 IU/day, or to a placebo [14, 55]. There was no attempt at randomisation between the two vitamin E dosage groups, and the study did not plan to examine dose-response effects. More than 90% of patients had angina, evidence of reversible cardiac ischaemia or both, although these characteristics were not required. Almost all subjects were recruited on the day of their admission immediately after elective angiography. There were no exclusion criteria, except prior use of vitamin supplementation containing vitamin E. Patients who had received α-tocopherol supplementation experienced a combined risk of fatal and non-fatal AMI only one-half that experienced by the placebo group. When non-fatal and fatal events were separated, patients with supplementation had an event rate of non-fatal AMI that was only 20% of that in the placebo group.

Davey et al. [14] conducted a cost-effective analysis of vitamin E supplementation in patients with coronary artery disease using CHAOS data. Cost-effectiveness in Australia and USA was compared. Clinical outcome was the incidence of non-fatal AMI. Utilisation was based on a survey of Australian clinicians and published Australian and USA cost data. Cost savings of US$ 127 (A$ 181) and US$ 578 per patient randomised to vitamin E therapy compared with placebo were found for Australia and USA respectively. Vitamin E group savings were due primarily to reduction in hospital admissions for AMI. The vitamin E group had a 4.4% lower absolute risk of AMI than the placebo. Less than 10% of health care costs in Australia was due to vitamin E (US$ 150 per patient, A$ 214). Davey et al. [14] initially calculated costs for Australian hospitals and drugs in Australian dollars, which they reported. They then applied an adjustment factor of 0.70 to calculate the US dollars. Since the authors had originally reported Australian costs on this basis, there was no need to further adjust the data. The costs shown above are those reported by Davey et al. The conversion of Australian dollars into American dollars appears to be based on an exchange rate rather than a HPPP conversion.

Vitamin E therapy in patients with angiographically confirmed atherosclerosis is cost-effective in Australia and USA [14]. The USA guidelines make no reference to the cost-effectiveness study undertaken by Davey et al. [14]. Any further revisions should include such information in the review. The findings of the CHOAS trial differed from those of the Heart Outcomes and Prevention Evaluation study by Lonn et al. [29], which found that vitamin E, relative to Ramipril, was effect-neutral on the progression of atherosclerosis in patients aged over 55 years with vascular disease or diabetes and one other risk factor but without heart failure or left ventricular ejection fraction. Ramipril had a beneficial effect on atherosclerosis progression. CHAOS is the only study to show a benefit of vitamin E. The results of all other studies have been negative. Therefore there is no confidence amongst cardiologists that there is any benefit.

Lipid management: pravastatin

Secondary coronary prevention with lipid-lowering drugs has become a major issue in health policy formulation due to the large up-front investment in drug therapy. The Swiss LIPID trial with pravastatin in secondary prevention raised the question of whether the drug is cost-effective. Szucs et al. [57] undertook a cost-effectiveness analysis from the perspective of third-party payers. Costs included daily treatment costs of pravastatin, non-fatal MI, CAGS and stroke. The net costs of treating 1000 patients (i.e. drug costs minus the costs of sequelae and interventions) were 3.6 million Swiss francs (A$ 2.09 million); 430 life years may be saved through treatment. The corresponding cost-effectiveness of pravastatin treatment is 8,341 Swiss francs (A$ 4,838) per life year saved, or 6,985 Swiss francs discounted. The cost-effectiveness of pravastatin in secondary prevention lie well within the threshold of other commonly accepted medical interventions and may be considered an economically viable approach for secondary coronary prevention. The USA guidelines make no reference to pravastatin, although other statins are considered. The study was graded as strong on both costs and effectiveness scores applying both the NHMRC grades of recommendation and the Drummond et al. [15] checklist and easily falls within the threshold criteria to recommend whether less than $70,000 per life year saved.

Conclusion

The USA guidelines require updating to include the following key findings relating to angioplasty, stents, various drugs and serum markers. We turn firstly to angioplasty. PTCA is cost-effective rela-

tive to tPA for men aged 60 years, with additional cost per life year saved of 274 ecu (A$ 308). PTCA with discharge after 3 days has been found to be cost-effective in low-risk AMI. With regard to ad hoc angioplasty, PTCA performed during the same sitting as diagnostic coronary angioplasty, called 'ad hoc' PTCA, has not demonstrated uniform cost savings for stable angina, unstable angina or post-MI, except where patients received stents. Some cost advantage of ad hoc angioplasty may occur where risks are low such as for stable angina or where stents are used, given they carry a reduced risk of complications.

There are several key findings relating to GPIIb/IIIa, thrombolytic, anticoagulant and antiarrthymic drugs. With regard to GPIIb/IIIa drugs, mean hospital costs (exclusive of drug costs) were equal for placebo, abciximab bolus, and abciximab bolus+infusion with incremental 6 month cost for the latter treatment averaging US$ 293 (A$ 302) per patient. Agent recouped almost all initial therapy costs with significant benefits. The incremental cost of abciximab per event prevented is US$ 3,258 ($ 3356). Tirofiban compared to placebo after high-risk angioplasty for AMI or unstable angina decreased the rate of hospital deaths, MI, revascularisation at 2 days by 36% relative to placebo (8% vs. 12%) without increased cost. Clinical benefits were similar at 30 days. When tirofiban+aspirin+heparin' was compared with 'heparin+aspirin', tirofiban had savings of 33,418 ecu (A$ 31,841) per 100 patients for the first 7 days of treatment.

A study concerning cost-effectiveness of thrombolytic treatment found that recombinant tPA is more cost-effective than streptokinase. Incremental costs for each life saved when streptokinase is substituted by recombinant tPA are 31%, 45%, 97% higher in Germany, Italy and USA than in the UK. Enoxaparin, an anticoagulant, is a promising alternative to unfractionated heparin for hospitalised patients with non-Qwave MI or unstable angina, saving Canadian $1,485 (A$ 1,708) per patient over 12 months, with 10% reduction in 1-year risk of death, MI or recurrent angina.

With regard to antiarrthymics, cost-effectiveness analysis comparing no amiodarone, amiodarone for patients with depressed heart rate variability (DHRV) and amiodarone for patients with DHRV plus positive programmed ventricular stimulation (PPVS) for high-risk post-AMI found that amiodarone for DHRV+PPVS patients was dominated by a combination of the two alternatives. Compared to no amiodarone, the incremental cost-effectiveness of amiodarone for DHRV patients in the USA was US$ 39,422 (A$ 39,816) per QALY gained. Amiodarone for DHRV is most appropriate.

A key study concerning serum markers found that adding automated cardiac troponin I assay (c-TnI) to a cardiac panel comprising CK-MB, myoglobin, total CK activity and a calculated CK-MB relative index resulted in significantly shorter length of stay and lower total and variable costs for low-risk patients. Average costs declined from US$ 6,170 (A$ 5,306) to US$ 4,550 (A$ 3,913) for this low-risk group. Secondary prevention through antioxidants and provastatin hold promise although further work on Australian cost-effectiveness studies are required before definitive implications can be reached.

A limitation of the study was that whilst the health PPP was effectively used to extrapolate findings into the Australian setting, more localised studies will shed light in the future. We plan such studies as the next step, which will be greatly facilitated by our access to high-quality costing data for our hospital and those of the Health Round Table benchmarking group that includes major teaching hospitals from Australia and New Zealand.

The results of the current study will be forwarded to the NHMRC and the relevant colleges in the United States, Canada and Europe for consideration in their updates of their CPGs on AMI. They are also being used locally to impact on health care delivery through the developmental process for protocols and clinical pathways.

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