National Horizon Scanning Unit
Horizon scanning report

TherOx® AO System: hyperoxemic perfusion for the treatment of microvascular ischaemia in patients with acute myocardial infarction

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Executive Summary

Acute myocardial infarction (AMI) or heart attack is the most common cardiovascular event in Australia, responsible for 47,000 public hospital separations in 2003-04 and approximately 15,000 deaths in the year 2000. AMI occurs when clots form in the coronary artery, severely restricting blood supply to the heart and causing the heart muscle to become ischaemic. To treat this, revascularisation of the heart should take place immediately. The blockage can be removed with standard treatments such as percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG).

The TherOx® aqueous oxygen (AO) system is designed as an adjunctive treatment and should take place after PCI or CABG, preferably within 24 hours of AMI symptom onset. Aqueous oxygen has approximately ten times the oxygen carrying capacity of blood (1-3ml O\textsubscript{2}/ml saline). The AO solution is mixed with the patient’s own blood and delivered in a closed system, via a coronary catheter, to the site of ischaemic injury at a partial pressure (pO\textsubscript{2}) of >600 mm Hg.

There is limited literature available describing the results of treatment with the TherOx® AO system, with only two studies being included for assessment in this report. One peer reviewed study and several abstracts reported on the progress of the AMIHOT randomised controlled trial (Intervention level II evidence), which is scheduled for completion in 2005. A total of 269 AMI patients, presenting within 24 hours of symptom onset, were randomised to either treatment with AO or standard treatment alone. Patients were follow-up for three months. Complete results of this trial have not been reported as yet.

The high quality study by Warda et al (2005) reported the results of a subgroup of patients (n=50) within the AMIHOT trial, treated with AO following PCI within six hours of AMI symptom onset. Significant improvements were reported in left ventricular ejection fraction (LVEF) from baseline to end of follow-up within the AO treated group (p<0.05) and between the AO and control groups (p<0.05). Abstracts by Martin et al (2004b and 2005) reported a significant improvement in wall motion score indexes (WMSI) in the AO treated group when compared to the control group at three-months follow-up (p<0.01). Greater improvements in WMSI were reported for the subgroup of patients that underwent treatment within six hours of symptom onset (p<0.01).

The first human clinical pilot study (Intervention level IV evidence) reported on the use of TherOx® AO in 29 patients who had undergone percutaneous transluminal coronary angioplasty within 24 hours of AMI symptom onset (Dixon et al 2002). This study reported a significant improvement in LVEF at one and three month follow-up (p<0.01), in addition to significant improvement in WMSI as early as 24 hours post-AO treatment (p<0.01).
Mortality was reported in the study by Warda et al (2/24, 8.3%), however death was due to complications of the PCI procedure and deemed not to be associated with the AO treatment. The most serious adverse event occurred when one patient (3.4%) required a blood transfusion after excessive bleeding at the femoral access site for AO catheterisation.

In summary, results indicate that the TherOx® AO system appears to be effective in increasing left ventricular ejection fraction and decreasing the wall motion score index when compared to standard treatment alone, for patients presenting within 24 hours of AMI symptom onset. This indicates improvement in left ventricular function. Patients who are treated within six hours of AMI symptom onset demonstrate even greater improvement in left ventricular function. Studies included in this assessment had short-term follow-up (3 months) (see Appendix C). In addition, these studies did not report any data regarding the quality of life of patients after AO treatment. Treatment with AO demonstrated short-term improvements in heart function following ischaemia; however what the improvement in LVEF and WMSI means for patient survival in the long term is unclear from these results.

There are currently no cost-effectiveness data available for the utilisation of the TherOx® AO system. However, as this therapy supplements, rather than replaces standard treatments there is likely to be additional costs to the health system. Whether this is balanced against additional long-term survival gains or a reduction in morbidity is currently unclear.

It would be prudent to await the complete results of the AMIHOT trial, which are expected in late 2005.
From the evidence presented in this report it would appear that the Therox® Aqueous Oxygen system had marginal benefits for patients experiencing an acute myocardial infarction, who were treated within 24 hours of symptom onset. The Committee noted that the results of a randomised controlled trial of this technology would be made available in late 2005 and that it would be wise to await these results.
The National Horizon Scanning Unit, Department of Public Health, University of Adelaide, on behalf of the Medical Services Advisory Committee (MSAC), has undertaken an Horizon Scanning Report to provide advice to the Health Policy Advisory Committee on Technology (Health PACT) on the state of play of the introduction and use of the TherOx® AO System (Horizon Scanning Register number: 000142).

TherOx Inc. provide the TherOx® AO hyperoxemic perfusion system for the treatment of microvascular ischaemia in patients with acute myocardial infarction. The TherOx® AO System is approved for sale in Europe but is currently unavailable in Australia.

This Horizon Scanning Report is intended for the use of health planners and policy makers. It provides an assessment of the current state of development of the TherOx® AO System, its present use, the potential future application of the technology, and its likely impact on the Australian health care system.

This Horizon Scanning Report is a preliminary statement of the safety, effectiveness, cost-effectiveness and ethical considerations associated with the TherOx® AO System.

Background

Description of the technology

The procedure

Coronary recanalisation is recommended for acute myocardial infarction (AMI) patients as early in the treatment protocol as possible to re-establish blood flow to ischaemic myocardial tissue. Impaired microvascular perfusion may still occur despite rapid and complete restoration of blood flow, resulting in additional injury to the myocardium, poor recovery of left ventricular function and a worsened clinical outcome. TherOx® AO proposes a potential role for high concentrations of oxygen delivered directly to the coronary artery to reduce microvascular injury (Bartorelli 2003; Glazier 2005).

Aqueous oxygen (AO) is a physiologic solution that contains high concentrations of dissolved oxygen (1-3ml O₂/ml saline), approximately ten times greater than the oxygen-carrying capacity of arterial blood. Depending on the application, the amount of oxygen in AO can be varied (Bartorelli 2003). Cavitation, or bubbling of a solution, usually requires a surface on which to nucleate (this surface can be provided by the side of a container) and may also be caused by a drop in the local ambient pressure below the vapour pressure (Wikipedia 2005). The TherOx® AO
system avoids cavitation with the use of silica capillary tubes and the application of high hydrostatic pressures. The stabilised AO solution can be mixed with the patient’s blood, creating a bubble-free hyperoxemic blood perfusate which can be infused intra-arterially (Bartorelli 2003).

The TherOx® AO system consists of a disposable, single use, three-chamber AO cartridge, a computerised pump and control housing and the AO delivery catheter. The first chamber of the AO cartridge is called the ‘piston chamber’ as it introduces the saline solution into the second, ‘atomiser’ chamber, where oxygenation of the saline solution takes place using medical grade oxygen. The AO solution then flows into the third, ‘blood-mixing’ chamber at a rate of 3.5 ± 1.5 ml/min. The fluid pathway has two separate lines, one for drawing the patient’s blood and the other for returning the hyperoxemic blood, and transducers measure the pressure in both of these lines. The hyperoxemic blood is delivered in a controlled manner by the delivery catheter placed directly at the site of ischaemic injury. The rate of flow is controlled by the computerised pump.

Figure 1 is a schematic representation of the TherOx® AO system in use. Patients are treated with the TherOx® AO system for a 90 minute period (Bartorelli 2003).

The TherOx® AO system does not require preparation by a perfusionist and the system can be set up in approximately five minutes. Patients are routinely administered an intravenous bolus of heparin ranging from 7000-10,000 IU at the beginning of the procedure, with a repeat intravenous bolus of 2500-5000 IU during the 90-minute procedure, maintaining the activated clotting time between 250 and 300 seconds. The hyperoxemic blood delivered by the AO system has a partial pressure (pO\textsubscript{2}) of >600mm Hg. Full saturation of haemoglobin occurs at a pO\textsubscript{2} of 100mm Hg, however the oxygen content of blood increases by >2 per cent by volume when the pO\textsubscript{2} increases from normoxemic levels to above 600mm Hg due to the increased dissolution of oxygen in plasma. By delivering high levels of oxygen in the plasma, the TherOx® system has the potential to increase the diffusion of oxygen into the ischaemic myocardium (Bartorelli 2003).
Intended purpose

The TherOx® AO system is intended to treat patients who have experienced acute myocardial infarction (AMI), resulting in oxygen deprivation and damage to myocardial tissue (Figure 3). AMI, more commonly referred to as a heart attack, is regarded as an irreversible injury to the heart muscle (Antman & Braunwald 2001; Mathur 2002). The TherOx® AO system is designed to be used as an adjunct to current interventional therapies, including stenting, coronary angioplasty, and other interventional procedures.

The underlying cause of AMI is atherosclerosis, which results in the build up of plaques in the lumen of coronary arteries. Risk factors such as hypertension, tobacco smoking, high blood cholesterol, obesity, insufficient physical activity and poor diet may result in the development of vascular injury, plaques and the subsequent development of a coronary artery thrombus. Infarction occurs when an atherosclerotic plaque suddenly breaks, fissures or ulcerates, initiating
thrombogenesis or activation of the coagulation cascade. Thrombogenesis may result in the production of a clot, leading to the thrombotic occlusion of the coronary arteries, resulting in a sudden decrease in coronary blood flow (Antman & Braunwald 2001; Mathur 2002).

Patients suspected of suffering AMI will undergo a diagnostic electrocardiogram (ECG) in addition to a blood test for the detection of serum cardiac enzymes (Antman & Braunwald 2001). During acute myocardial infarction, a central area of necrosis is normally surrounded by an area of injury, which in turn is surrounded by an area of ischaemia (Figure 3) (American Heart Association 2005). Ischaemic or necrotic tissue alters the electrical properties of myocardial cells, altering the signals detected by an ECG. The distinction between ischaemia and necrosis is whether the event is reversible. Transient myocardial ischaemia that produces T wave, and sometimes ST segment abnormalities, can be reversible without producing permanent damage and is not accompanied by serum enzyme elevation (American Heart Association 2005; Antman & Braunwald 2001; Goldberger 2001).

In addition to the treatment of patients experiencing AMI, the TherOx® AO system may have potential applications in stroke patients, cancer therapy, wound and skin care treatment, organ preservation, and haemorrhagic shock. Potentially, AO may be a treatment for all types of ischaemia (Therox Inc 2003).

Clinical need and burden of disease

In Australia, the age-standardised rate of acute myocardial infarction public hospital admissions has been steadily decreasing since the early 1990s, corresponding to a decline in the incidence of AMI. However, the absolute number of admissions has remained steady or increased due to the increasing average age and overall growth of the population. In Australia, AMI occurs predominantly amongst those aged 40 years and over (97 per cent), with almost two-thirds occurring among people aged 65-90 years of age. Men are twice as likely to be admitted than women (Figure 4) (Mathur 2002).

The number of public hospital separations for patients with acute myocardial infarction, in 2003-04, was 46,885. Of these, there were 30,795 male and 16,089 female separations, representing a total of 270,125 patient days. This equates to a rate of 519 separations per 100,000 population, aged 40 years and over.1

1 Total population in Australia was 19,872,646 and the population aged 40 years and over was 8,819,746 as at June, 2003. Source: Australian Bureau of Statistics.
One in four Australians experiencing a heart attack or AMI will die within an hour of the first symptoms and almost nine in ten coronary deaths will occur before the patient reaches hospital. In Australia, the National Cardiovascular Disease and Diabetes Database recorded that in the year 2000, 14,616 persons died from AMI at a rate of 76.3 per 100,000 (AIHW 2005). Of these, 3,258 patients died in hospital from AMI, representing 12 per cent of all AMI patients. During this same period, women aged 40-90 years admitted to hospital with AMI were more likely to die during the acute admission period than men of the same age (after adjusting for age). Crude in-hospital, case-fatality rates were 16 and nine per cent for women and men, respectively. In-hospital, case-fatality rates increase rapidly with increasing age from approximately four per cent amongst 40-64 year olds to 10 per cent in 65-74 year olds and 20 per cent in 75-90 year olds (Mathur 2002).

Patients experiencing AMI require prompt and complete restoration of blood flow in the infarcted artery, i.e. reperfusion. Reperfusion strategies for patients who have experienced AMI include pharmacological treatment, percutaneous coronary intervention (PCI) or surgical measures such as a coronary artery bypass graft (CABG) surgery (American Heart Association 2005). Of the patients admitted to acute care hospitals in 1999-00, 30 per cent received either cardiac catheterisation, PCI or CABG. Patients who underwent cardiac catheterisation, PCI or CABG during acute admission were less likely to die in hospital that AMI patients overall (11.6 per cent) (Mathur 2002).

Cardiac catheterisation or angiography is used to identify the location of any coronary blockages (Mathur 2002). In the year 1999-00, 74,293 of these
procedures were performed at a rate of 390 per 100,000 population (AIHW 2005). The in-hospital case-fatality rate for patients undergoing cardiac catheterisation was 3.1 per cent during this same period (Mathur 2002).

Percutaneous coronary intervention is a term used to describe all forms of percutaneous revascularisation, including coronary artery stenting and percutaneous transluminal coronary angioplasty (PTCA) (Mathur 2002). In the year 1999-00, 20,739 coronary angioplasty procedures were performed at a rate of 109 per 100,000 population (AIHW 2005). The in-hospital case-fatality rate for patients undergoing coronary angioplasty was 3.5 per cent during this same period (Mathur 2002).

Coronary artery bypass grafting is an invasive procedure which uses veins taken from the patient’s legs to bypass the obstructed coronary arteries. In 1998 the average number of bypass grafts was three per patient and six per cent of CABGs were for re-operations (Mathur 2002). In the year 1999-00, 17,301 CABGs were performed at a rate of 91 per 100,000 population (AIHW 2005). The in-hospital case-fatality rate for patients undergoing coronary angioplasty was 5.4 per cent during this same period (Mathur 2002).

In New Zealand, the number of public hospital separations for patients with acute myocardial infarction, in 2002-03, was 11,582 and of these, there were 7,272 male and 4,310 female separations. Provisional 2002 data reported 3,252 deaths with an underlying cause of AMI.²

Stage of development

The TherOx® AO aqueous oxygen system is currently approved for investigational use only by the United States’ Food and Drug Administration. It has been approved for use in Europe since 2002. The TherOx® AO aqueous oxygen system has not been registered by the Australian Therapeutic Goods Administration. However, given that there are no other existing treatments which act as an adjunct to angioplasty, and the high number of potential patients, it is likely that there will be a rapid uptake of this technology in Australia if it is introduced.

Treatment Alternatives

Existing comparators

Initial general treatment measures (during the first few hours) for patients suspected of experiencing an AMI include the administration of:

² Data supplied by Chris Lewis from New Zealand Health Information Service. Total population of New Zealand for the year 2003 was 4,009,200.
• oxygen, usually by nasal prongs, if arterial oxygen <90%, which may limit ischaemic myocardial injury;
• nitroglycerin, to relax the coronary arteries, potentially improving blood flow;
• analgesia, usually in the form of morphine (2-4 mg), as acute pain may contribute to increased sympathetic activity through heightened anxiety levels;
• chewable aspirin (160-325 mg), where not contraindicated by individuals with hypersensitivity to salicylate, which inhibits thromboxane A₂ production;
• beta-blocking agents, to diminish myocardial oxygen demand by reducing the heart rate, systemic arterial pressure and myocardial contractility; and
• angiotensin-converting enzyme (ACE) inhibitor, to relax blood vessels, lower blood pressure and increase the supply of blood and oxygen to the heart (American Heart Association 2000; Antman et al 2004).

For patients who have a persistent blockage of the coronary artery, reperfusion or revascularisation (restoring adequate blood flow to the ischaemic myocardium) should be initiated as soon as possible. The choice of reperfusion therapy will depend on the location of the patient and the available medical staff. Reperfusion procedures include thrombolysis, percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) (Mathur 2002).

Intravenous thrombolysis has been demonstrated to establish reperfusion in 50-90 per cent of patients and to reduce mortality by 30-40 per cent, compared to placebo. Thrombolytic agents, such as streptokinase, anisoylated plasminogen-streptokinase activator complex and recombinant tissue-type plasminogen activator, activate plasminogen to form plasmin. Plasmin promotes the lysis of fibrin within the coronary thrombi, resulting in reperfusion. However, thrombolytic agents may be associated with an increased incidence of haemorrhage as thrombolytic agents are unable to differentiate between “good” (eg plugging of cerebrovascular leak) and “bad” clots (Gossage 1994).

Before PCI or CABG can be performed, cardiac catheterisation is necessary to identify the location of the coronary blockages. A catheter is inserted through the blood vessels to the heart and the coronary arteries, releasing a dye, enabling visualisation of the arteries under X-ray (Mathur 2002).

PCI involves inserting a catheter with a balloon at the point where the coronary artery has been narrowed by a plaque, then inflating the balloon, reducing or removing the obstruction. Studies have demonstrated that PCI results in higher rates of coronary patency and lower rates of recurrent ischaemia and re-infarction compared to thrombolysis. Recent advances include the implantation of coronary stents, which expand within the artery at the point of narrowing, reducing the
incidence of abrupt vessel closure in the months following the PCI procedure (Bartorelli 2003; Mathur 2002). In addition, beneficial improvements in the microcirculation have been obtained with the use of either thienopyridines and glycoprotein IIb/IIIa receptor antagonists during percutaneous coronary interventions (Bartorelli 2003; Glazier 2005).

CABG utilises blood vessel grafts (usually the saphenous vein) to bypass blockages in the coronary arteries to restore adequate blood supply to the heart (Mathur 2002).

Hyperbaric oxygen therapy (HBOT) has also been evaluated as a means of delivering high concentrations of oxygen directly to the coronary artery, thus reducing microvascular injury (Bartorelli 2003; Glazier 2005). HBOT involves the intermittent inhalation of 100 per cent oxygen in chambers pressurised above one atmosphere absolute. One atmosphere absolute is defined as the atmospheric pressure at sea level and is equivalent to 101.3 kiloPascals (kPa) or about 14.7 pounds per square inch. However, a MSAC report, completed in 2000, reported that there was no firm evidence to support the use of HBOT for the treatment of AMI. There was some indication that HBOT used in conjunction with thrombolytic therapy may be beneficial in pain relief. The MSAC report concluded that public funding for HBOT should not be supported for this indication (Villanueva et al 2001).

In addition there are other methods currently being trialled to limit reperfusion injury:

- Calderet in ST-elevation myocardial infarction (CASTEMI) trial. AMI patients are infused with calderet, an agent which reduces intracellular calcium levels by inhibiting the sodium/calcium exchange and increasing uptake into the sarcoplasmic reticulum. In this trial there was no difference between the treatment group and the control group in the primary endpoint (size of infarct after seven days). A larger clinical trial (EVOLVE) is in progress in the United States (O'Neill et al 2005).

- Clinical trial of metabolic modulation in acute myocardial infarction treatment evaluation - Estudios Cardiológicos Latinoamérica (CREATE-ECLA). AMI patients receive a high dose glucose-insulin-potassium infusion to treat cardiac ischemia. In this trial there was no difference between the treatment group and the control group in the primary endpoint (mortality) or for secondary endpoints, including re-infarction (O'Neill et al 2005).

- Intravascular cooling adjunctive to primary coronary intervention (ICE-IT) trial. In this trial, patients were randomised to receive hypothermia or standard treatment. The hypothermia group were cooled with an endovascular cooling catheter for six hours. There
was no difference in the final infarct size in the hypothermia group (O'Neill et al 2005).

**Clinical Outcomes**

Horizon Scanning reports generally do not consider or appraise animal studies, however due to the scarcity of literature describing the use of the TherOx® AO system in humans, a short précis of animal studies is presented. Several animal studies report initial results using hyperoxemic perfusion with aqueous oxygen.

Early experimental work in rabbits tested the hypothesis that intra-arterial delivery of AO was capable of correcting hypoxemia. Animals in the intervention group received AO via the mid-abdominal aorta at 1gm/min (n=15). Control animals received saline only (n=7). The mean distal arterial pO$_2$ increased from 70 ± 10 mm Hg at baseline to 236 ± 113 mm Hg after one hour of air breathing and to 593 ± 114 mm Hg after 100 per cent oxygen breathing ($p<0.01$). No effect on pO$_2$ was noted in the control group. In addition no differences were noted in blood counts and chemistries between the control and treatment groups. The authors concluded that intra-arterial infusion of AO was effective in the regional correction of hypoxemia (Spears et al 1997b). Similar results were reported by Corno et al (2004) who studied the effects of AO on hypoxia in calves (Corno et al 2004a; Corno et al 2004b).

A later study by Spears et al (2002) reported on the results of intra-coronary AO hyperbaric reperfusion in swine following a 60-minute balloon occlusion of the left anterior descending coronary artery. Intra-coronary AO hyperoxemic perfusion (mean pO2 = 834 104 mmHg), delivered via a catheter to the blockage site, was performed for 90 minutes after a 15-minute period of normoxemic autoreperfusion (physiologic reperfusion). Control groups consisted of autoreperfusion alone; active normoxemic perfusion (50 ml/minute) for 90 minutes; and hyperoxemic perfusion with a hollow fibre oxygenator for 90 minutes. After three hours reperfusion, evaluation of the infarct area at post-mortem demonstrated that endothelial oedema and associated capillary luminal narrowing were prominent in the tissue of controls but not in the AO treated animals. The authors concluded that intra-coronary hyperbaric reperfusion with AO, but not with a membrane oxygenator, attenuates myocardial ischaemia/reperfusion injury (Spears et al 2002).

An abstract presented by Spears et al reported the initial results of experimental reperfusion in dogs. Occlusion of the coronary artery was experimentally induced in anaesthetised dogs for 90 minutes. The control group (n=7) underwent autoreperfusion (mean pO2=105 +/- 8 mmHg), while the intervention group (n=7) was perfused with hyperoxemic blood (pO2=512 +/- 158 mmHg) at 100 ml/min. for 60-90 min. The left ventricular ejection fraction increased significantly in the hyperoxemic perfused group compared to the control group ($p < 0.05$), and this
improvement was unchanged 30 minutes post-perfusion. No significant differences \( (p > 0.05) \) between the two groups were noted in other haemodynamic parameters or in microsphere collateral blood flow during occlusion (Spears et al 1997a). These results were later written up in a peer reviewed article, however at the time of writing the reviewers were unable to access this paper (Spears et al 2003).

**Effectiveness**

Two abstracts reporting on initial results of the AMIHOT study focussed on safety outcomes. Patients who were randomised to AO treatment \( (n=85) \) experienced no haemodynamic or electrophysiologic instabilities during AO infusion and no adverse events were reported as being associated with the procedure (Martin et al 2003a; Martin et al 2003b).

The first human clinical pilot study using the TherOx® AO system was a multi-centre case series conducted by Dixon et al on 29 patients who had all undergone PTCA within 24 hours of symptom onset, followed by treatment with AO (Dixon et al 2002). This study reported on aspects of the AO treatment (Table 1), the haemodynamic parameters of the patient before and after treatment with AO (Table 2) and length of hospital stay (Table 4).

This study reported a significant increase in the mean arterial \( pO_2 \) from baseline to the end of the 90 minute AO-treatment period \( (p=0.01) \) (Table 2). In addition there was a small but significant decrease in mean pulmonary wedge pressure at the end of the infusion period compared to baseline \( (p=0.04) \), which the author suggests demonstrates an improvement in left ventricular function.
Table 1  Characteristics of AO procedure

<table>
<thead>
<tr>
<th>Study</th>
<th>Level of Interventional Evidence</th>
<th>Study Design</th>
<th>Population</th>
<th>Outcomes</th>
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<tbody>
<tr>
<td>Dixon et al (2002)</td>
<td>IV</td>
<td>Case series</td>
<td>29 patients with AMI, all underwent PTCA with (93%) or without (7%) stenting. 76% received glycoprotein receptor antagonist</td>
<td>26/29 (89.6%) patients had successful angiography post-AO (TIMI grade 3 flow) 29/29 (100%) successful hyperoxemic infusion Mean infusion time 80 ± 18.2 min Mean loop flow 82 ± 13 ml/min pO2 perfusate 631 ± 235 mm Hg</td>
</tr>
<tr>
<td>Warda et al (2005)</td>
<td>II</td>
<td>RCT Sub-group of AMI HOT trial</td>
<td>50 patients with AMI (anterior) underwent PCI within 6 hours of symptom onset. Randomised to AO infusion (n=24) or standard care (n=26)</td>
<td>Mean infusion time 83 ± 21 min</td>
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PTCA = percutaneous transluminal coronary angioplasty

Table 2  Haemodynamic parameters before and after AO infusion

<table>
<thead>
<tr>
<th>Study</th>
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<tbody>
<tr>
<td>Dixon et al (2002)</td>
<td>IV</td>
<td>Case series</td>
<td>29 patients with AMI, all underwent PTCA with (93%) or without (7%) stenting. 76% received glycoprotein receptor antagonist</td>
<td>Baseline BP systolic 124 ± 16.4 122.8 ± 17.3 BP diastolic 80.5 ± 11.2 80.7 ± 11.9 Heart rate’ 78.4 ± 11.3 73.2 ± 14.9 PA systolic 36.2 ± 12.7 31.3 ± 10.3 PA diastolic 19.3 ± 5.3 16.3 ± 5.4 PCW 21.4 ± 9.0 16.0 ± 6.9 Systemic pO2 149.4 ± 73.6 166.7 ± 78.6 Loop pO2” 631 ± 235.7 751 ± 188.4</td>
</tr>
</tbody>
</table>

AO = aqueous oxygen, BP = blood pressure (mm Hg). All measurements are in mm Hg. *Heart rate = beats/min, †Loop pO2 = pO2 of blood infused into the infarct-related artery via the distal portion of the aqueous oxygen system circuit, PA = pulmonary artery pressure, PCW = pulmonary capillary wedge pressure

Assessment of left ventricular (LV) function following AMI may be used to give prognostic information to guide therapy. Two-dimensional ECG data of left ventricular ejection fraction (LVEF) and wall motion score index (WMSI) are both markers of LV dysfunction (Galasko et al 2001). Left ventricular ejection fraction is the ratio of stroke volume to end diastolic volume (normal value 67 ±
8%) (Braunwald 2001). Damage to the myocardium will result in a reduced LVEF. WMSI is arrived at by dividing the LV wall into 16 segments and regional wall motion is scored for each segment. Segments are graded: 1= normal, 2= hypokinetic, 3= akinetic and 4= dyskinetic. The WMSI is equal to the sum of the segment scores divided by the number of segments scored (Dixon et al 2002). WMSI correlates well with LVEF (Galasko et al 2001). Improvements in LV function will therefore be reflected in an increase in LVEF and a decrease in the WMSI, from baseline values.

Changes in LV function were reported in the case series conducted by Dixon et al (2002) (Intervention level IV evidence). In addition, the remaining peer-reviewed paper by Warda et al (2005) and two abstracts (Martin et al 2004b; Martin et al 2005) reported LV function in differing numbers of patients enrolled in the AMIHOT trial (Intervention level II evidence) (Table 3).

The high quality study by Warda et al (2005) reported a significant increase in LVEF from baseline to one-month follow-up within the AO infused group ($p<0.05$). A slight decrease in LVEF was detected in the control group over the same period. In addition, the difference between the AO and control groups was significant ($p<0.05$). At one month, LV end-diastolic and end-systolic volumes significantly increased in the control group demonstrating LV remodelling, however, LV volumes remained unchanged in the AO group. These findings lead the authors to conclude that treatment with AO prevents LV remodelling and increases LVEF compared to standard therapy alone.

One abstract reported a significant improvement in WMSI in the AO treated group when compared to the control group at three-month follow-up ($p<0.01$) (Martin et al 2004b). The more recent abstract reported a significant improvement in the AO infused group from baseline to three-month follow-up ($p<0.03$). Greater improvements in WMSI were reported for the subgroup of patients who underwent treatment within six hours of symptom onset ($p<0.01$) (Martin et al 2005).
<table>
<thead>
<tr>
<th>Study</th>
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<tr>
<td>Warda et al (2005)</td>
<td>II</td>
<td>RCT</td>
<td>Sub-group of AMI/HOT trial</td>
<td>Adequate ECG images available for 20/24 (83.3%) of AO group 22/26 (84.6%) control group</td>
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<td>50 patients with AMI (anterior) underwent PCI within 6 hours of symptom onset</td>
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<td>Randomised to AO infusion (n=24) or standard care (n=26)</td>
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<td>One month follow-up</td>
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<td>LV end diastolic volume (ml)</td>
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<td>∆ within *</td>
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<td>Control 15 ± 23 p&lt;0.05</td>
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<td>AO -3 ± 26 NS</td>
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<td>∆ between ** p&lt;0.05</td>
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<td>LV end systolic volume (ml)</td>
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<td>∆ within *</td>
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<td>Control 10 ± 18 p&lt;0.05</td>
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<td>AO -7 ± 22 NS</td>
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<td></td>
<td>∆ between ** p&lt;0.01</td>
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<td>LVEF (%)</td>
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<td>∆ within *</td>
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<td>Control -1 ± 6 NS</td>
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<td></td>
<td>AO 5 ± 10 p&lt;0.05</td>
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<td>∆ between ** p&lt;0.05</td>
</tr>
<tr>
<td>Dixon et al (2002)</td>
<td>IV</td>
<td>Case series</td>
<td>29 patients with AMI, all underwent PTCA with (93%) or without (7%) stenting. 76% received glycoprotein receptor antagonist</td>
<td>Baseline and follow-up ECGs performed in 28/29 (96.5%) patients. 1/29 (3.5%) patients excluded due to technical difficulty</td>
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<td>Global LV function</td>
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<td></td>
<td></td>
<td>LVEF (%)</td>
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<td></td>
<td></td>
<td>Baseline 48.6 ± 7.3 p = 0.08, NS</td>
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<td></td>
<td>24 hrs 51.8 ± 6.8 p&lt;0.001</td>
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<td>1 month 54.4 ± 6.6 p&lt;0.001</td>
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<td>3 months 56.0 ± 8.3 p&lt;0.001</td>
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<td>WMSI</td>
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<td></td>
<td></td>
<td>Baseline 1.68 ± 0.24 p&lt;0.001</td>
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<td></td>
<td></td>
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<td>24 hrs 1.48 ± 0.24 p&lt;0.001</td>
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<td>1 month 1.39 ± 0.24 p&lt;0.001</td>
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<td></td>
<td>3 months 1.34 ± 0.26 p&lt;0.001</td>
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<td></td>
<td>Regional LV function</td>
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<td>WMSI of infarct region</td>
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<td></td>
<td></td>
<td>Baseline 2.18 ± 0.32 p&lt;0.001</td>
</tr>
<tr>
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<td></td>
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<td>24 hrs 1.84 ± 0.41 p&lt;0.001</td>
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<td>1 month 1.68 ± 0.44 p&lt;0.001</td>
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<tr>
<td></td>
<td></td>
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<td></td>
<td>3 months 1.63 ± 0.43 p&lt;0.001</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Sample Information</td>
<td>Intervention</td>
<td>Outcome Measures</td>
</tr>
<tr>
<td>-------------------------------</td>
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</tr>
</tbody>
</table>
| (Martin et al 2005)           | RCT    | 144 patients with AMI (anterior) underwent PCI within 24 hours of symptom onset | AO infusion (n=70) or standard care (n=74) | Improvement in WMSI | Improvement in WMSI; AO infused group
|                               |        |                    |              | Baseline | 0.78 ± 0.56 | 3 months | 0.57 ± 0.49 | p<0.03 |
|                               |        |                    |              | Subgroup patients treated within <6 hours symptom onset (n=40) | Baseline | 8.1 ± 0.58 *** | 3 months | 0.56 ± 0.48 | p<0.01 |
|                               |        |                    |              | ST-segment elevation, area under the curve | Area AO (%) | 47 | 35 | p=0.023 |
| (Martin et al 2004b)          | RCT    | 127 patients with AMI (anterior) underwent PCI within 24 hours of symptom onset | AO infusion (n=66) or standard care (n=61) | Regional WMSI, 3 months follow-up | Control | 2.21 ± 0.36 | AO | 1.95 ± 0.32 | p<0.01 |
|                               |        |                    |              | ST-segment elevation, area under the curve | Area AO (%) | 47 | 35 | p=0.023 |

LVEF = left ventricular ejection fraction, WMSI = wall motion score indexes, NS = not significant
* ∆ within = the difference between baseline and one month values within groups ± standard deviation, ** ∆ between = difference at one month between the AO and control groups, *** the WMSI value of 8.1 stated at baseline is higher than the stated values for WMSI (1-4). The author has been contacted but has not responded.
Table 4  Length of hospital stay

<table>
<thead>
<tr>
<th>Study</th>
<th>Level of Interventional Evidence</th>
<th>Study Design</th>
<th>Population</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dixon et al (2002)</td>
<td>IV</td>
<td>Case series</td>
<td>29 patients with AMI, all underwent PTCA with (93%) or without (7%) stenting. 76% received glycoprotein receptor antagonist</td>
<td>5.9 ± 2.9 days</td>
</tr>
</tbody>
</table>

PTCA = percutaneous transluminal coronary angioplasty

In summary, TherOx® AO system appears to be effective in increasing left ventricular ejection fraction and decreasing the wall motion score index when compared to standard treatment alone, for patients presenting within 24 hours of AMI symptom onset. This suggests an improvement in left ventricular function at 3 month follow-up. Patients who are treated within six hours of AMI symptom onset demonstrate an even greater improvement in left ventricular function at three month follow-up.

Safety

The high quality study by Warda et al (2005) reported two deaths which were attributed to factors not associated with AO infusion. One patient died of refractory heart failure within 12 hours after PCI. The other patient died one month after AMI due to complications of PCI for stenosis in the non-infarct related artery. The most serious adverse event was reported in the lower quality study by Dixon et al (Intervention level IV evidence), where one patient required a blood transfusion after bleeding in the femoral artery access site. This represents a serious operator error and the potential for considerable damage is real.
Table 5  Adverse events

<table>
<thead>
<tr>
<th>Study</th>
<th>Level of Interventional Evidence</th>
<th>Study Design</th>
<th>Population</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warda et al (2005)</td>
<td>II</td>
<td>RCT</td>
<td>Sub-group of AMIHOT trial 50 patients with AMI (anterior), underwent PCI within 6 hours of symptom onset Randomised to AO infusion (n=24) or standard care (n=26)</td>
<td>No complications were reported to be related to the AO infusion&lt;br&gt; AO-group 1/24 (4.2%) died of refractory heart failure within 12 hours of PCI 1/24 (4.2%) died after AMI due to complications of PCI for stenosis in the non-infarct-related artery within one month.</td>
</tr>
<tr>
<td>Dixon et al (2002)</td>
<td>IV</td>
<td>Case series</td>
<td>29 patients with AMI, all underwent PTCA with (93%) or without (7%) stenting. 76% received glycoprotein receptor antagonist</td>
<td>During hospitalisation period 1/29 (3.4%) required a blood transfusion due to bleeding at femoral access site 1/29 (3.4%) developed congestive heart failure, treated with conventional therapy 30 day follow-up No deaths, re-infarction, recurrent ischaemia or need for repeated target vessel revascularisation reported</td>
</tr>
</tbody>
</table>

AO = aqueous oxygen, PCI – percutaneous coronary intervention

Potential Cost Impact

Cost Analysis

There are currently no cost-effectiveness data available for the utilisation of the TherOx® AO system.

Simple costings

TherOx® AO is designed as an adjunct to standard treatment for AMI and should be used after standard procedures such as PCI have been performed. The cost of the TherOx® AO system is estimated to be approximately $US 35,000 ($AUD 46,484). The disposable components used for each patient cost approximately $US 2,000 ($AUD 2,656) (personal communication TherOx Inc). An MBS fee would be payable for the insertion of the catheter that delivers the oxygenated blood to the site of ischemia and for the supervision of the 90 minute AO treatment.

Currently there is no evidence to suggest that treatment with AO reduces the amount of time spent in hospital after AMI. The study by Dixon et al (2002) reported that patients treated with AO spent 5.9 ± 2.9 days in hospital. In 2003-04
there were 46,885 public hospital separations in Australia for AMI, representing 270,125 patient days. This equates to an average of 5.76 patient days per separation (Mathur 2002). However, treatment with AO may reduce the extent of LV injury, the number of re-infarctions or recurrent ischaemia, and in so doing may reduce the overall costs of AMI on the health system.

Ethical Considerations

Ethical issues related to using experimental therapies

The key ethical issue for the TherOx® AO system at this stage is the relatively experimental nature of the therapy. There is limited literature describing the results of treatment with the TherOx® AO system available, with only two studies being included for assessment in this report. There is an important, but debated, distinction in clinical ethics between experimental and established treatments (King 1995). Traditionally, an experimental treatment has been that which departs from established or orthodox treatments. More recently, some scholars have opted for a definition that focuses specifically on the issue of the availability of evidence. On this view, an experimental treatment is that for which there is insufficient evidence currently to demonstrate its benefits for patients (Tonelli et al 1996; Schneiderman & Jecker 1996). Given the current state of evidence about the TherOx® AO system, it is reasonable to class this treatment as experimental at this stage.

There are a number of dangers for patients if experimental treatments are adopted and disseminated too early (Tonelli et al 1996). First, if the treatment eventually turns out to be more harmful than helpful, premature adoption of the new technology harms a great deal more patients than would be harmed through continuation of trials. Second, early adoption increases the likelihood that it will not be possible to continue to evaluate the effectiveness of the new treatment. “Proliferation of unproved therapies raises the cost of health care and may divert funds from programs or therapies that are less dramatic, but more effective” (Tonelli et al 1996).

There are a few situations in which early adoption of unproven technologies may be ethically acceptable. The most compelling of these relate to situations in which patients have serious and life-threatening illnesses for which there are no alternative effective treatments (Beauchamp & Childress 2001). Since there are established treatments available for the treatment of AMI, it does not seem ethically acceptable to expose patients to this technology at this stage.

Informed Consent

Patients offered treatment with the TherOx® AO system must be fully informed of the potential benefits and harms associated with this treatment, especially in view of the experimental nature of the technology, compared to the usual practice of
medical therapy alone. Patients suffering an acute myocardial infarction are likely to be experiencing high levels of pain, confusion, stress and anxiety, and as such may find it difficult to make an informed decision about what may be considered a potentially risky procedure. The TherOx procedure represents a “Catch-22” situation as it cannot be performed on a healthy population capable of giving reasoned consent but instead relies on being performed on a vulnerable group of patients. Studies assessed in this report indicate that the TherOx® AO procedure, in a human clinical situation, is relatively new. These studies were multi-centred and had small numbers of patients enrolled, raising the issue of training lag time. It may be a considerable length of time before other practitioners become proficient at this procedure and able to get results similar to those produced in the small clinical trials.

Access Issues

TherOx® AO is likely to be accessible in only large, tertiary hospitals or centres of excellence where PCI and CABG procedures are routinely performed by specialist cardiologists. As this technology should ideally be administered within 24 hours of the onset of AMI symptoms, it would be highly unlikely to benefit individuals living in rural or remote areas.
Training and Accreditation

Training
Clinicians and nursing staff would be required to undergo training in the use and principles of operation, of the TherOx® AO system. Appropriate medical staff would be required to monitor patients and be able to interpret ECG readings taken during the AO procedure.

Clinical Guidelines
There are no current Australian guidelines for the treatment of AMI. The National Health and Medical Research Council (NHMRC) produced guidelines for the treatment and management of coronary heart disease in 1996, however these guidelines were rescinded in 2004. The NHMRC no longer endorses, supports or approves these guidelines (NHMRC 1996). The American College of Cardiology Foundation and the American Heart Association produced a comprehensive set of guidelines for the management of patients with ST-elevation myocardial infarction in 2004. These guidelines cover the management of patients prior to admission to hospital, during admission to the emergency department, suitable treatments prior to definitive diagnosis, treatment options in the acute, convalescence and discharge stages of myocardial infarction (Antman et al 2004).

Limitations of the Assessment
Methodological issues and the relevance or currency of information provided over time are paramount in any assessment carried out in the early life of a technology.

Horizon Scanning forms an integral component of Health Technology Assessment. However, it is a specialised and quite distinct activity conducted for an entirely different purpose. The rapid evolution of technological advances can in some cases overtake the speed at which trials or other reviews are conducted. In many cases, by the time a study or review has been completed, the technology may have evolved to a higher level leaving the technology under investigation obsolete and replaced.

An Horizon Scanning Report maintains a predictive or speculative focus, often based on low level evidence, and is aimed at informing policy and decision makers. It is not a definitive assessment of the safety, effectiveness, ethical considerations and cost effectiveness of a technology.

In the context of a rapidly evolving technology, an Horizon Scanning Report is a ‘state of play’ assessment that presents a trade-off between the value of early,
uncertain information, versus the value of certain, but late information that may be of limited relevance to policy and decision makers.

This report provides an assessment of the current state of development of the TherOx® AO system, its present and potential use in the Australian public health system, and future implications for the use of this technology.

**Search Strategy used for the Report**

The medical literature (Table 6) was searched utilising the search terms outlined in Table 7 to identify relevant studies and reviews, until July 2005. In addition, major international health assessment databases were searched (Appendix C).

**Table 6   Literature sources utilised in assessment**

<table>
<thead>
<tr>
<th>Source</th>
<th>Location</th>
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<tr>
<td><strong>Electronic databases</strong></td>
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<td>AustHealth</td>
<td>University library</td>
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<tr>
<td>Australian Medical Index</td>
<td>University library</td>
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<tr>
<td>Australian Public Affairs Information Service (APAIS) - Health</td>
<td>University library</td>
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<tr>
<td>Cinahl</td>
<td>University library</td>
</tr>
<tr>
<td>Cochrane Library – including, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, the Cochrane Central Register of Controlled Trials (CENTRAL), the Health Technology Assessment Database, the NHS Economic Evaluation Database</td>
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<tr>
<td>Current Contents</td>
<td>University library</td>
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<tr>
<td>Embase</td>
<td>Personal subscription</td>
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<tr>
<td>Pre-Medline and Medline</td>
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<td>University library</td>
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<td>PsycInfo</td>
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<tr>
<td>Websites of Specialty Organisations</td>
<td>Appendix C</td>
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Table 7  Search terms utilised

<table>
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<tr>
<td>MeSH</td>
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<td>Myocardial infarction; myocardial reperfusion; salvage therapy; infusions, intra-arterial; oxygen/administration and dosage; oxygen/therapeutic use</td>
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<tr>
<td>Text words</td>
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<tr>
<td>Myocardial infarction, acute myocardial infarction, aqueous oxygen, Therox</td>
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<tr>
<td>Limits</td>
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<tr>
<td>English, human</td>
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**Availability and Level of Evidence**

There were only two full length, peer reviewed papers included in this report to assess the safety and effectiveness of the TherOx® AO system for the treatment of AMI. One of these studies was a high quality study (Intervention level evidence II) reporting on outcomes of the AMIHOT study (Warda et al 2005). The remaining study was of lower quality (Intervention level IV evidence) (Dixon et al 2002). In addition six abstracts reported updated results of the AMIHOT trial (Martin et al 2004a; Martin et al 2003a; Martin et al 2003b; Martin et al 2004b; Martin et al 2005; O'Neill, 2004 #3012). Two of these abstracts were cited as being presented at the same conference but were published in different journals by different authors (Martin et al 2004a; O'Neill 2004).

Profiles of these studies are provided in Appendix B.

**Sources of Further Information**

The TherOx® AO aqueous oxygen system does not currently have approval from the United States Food and Drug Administration, however as of 2005, TherOx Inc are conducting human trials in order to gain pre-market approval (personal communication TherOx Inc). TherOx Inc is also currently conducting a European clinical study for the treatment of AMI using the TherOx® AO System.

**Conclusions**

Acute myocardial infarction (AMI) or heart attack is the most common form of heart disease in Australia, responsible for 47,000 public hospital separations in 2003-04 and approximately 15,000 deaths in the year 2000.

AMI occurs when clots form in the coronary artery, severely restricting blood supply to the heart and causing the heart muscle to become ischaemic.

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3 AMIHOT is the Acute Myocardial Infarction Hyperbaric Oxygen Treatment trial
Prompt treatment is required to revascularise the heart by removing the blockage, with standard treatments such as percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery. The TherOx® aqueous oxygen (AO) system is designed as an adjunct in the treatment of AMI. Treatment with the TherOx® system should take place after PCI or CABG and ideally within 24 hours of AMI symptom onset. Reduced oxygen flow to the heart may result in damage to the myocardial tissue. The TherOx® AO system delivers high concentrations of oxygen directly to the damaged myocardial tissue to reduce further microvascular injury. Aqueous oxygen has approximately ten times the oxygen carrying capacity of blood (1-3ml O₂/ml saline). The AO solution is mixed with the patient’s own blood and delivered via a coronary catheter to the site of ischaemic injury at a partial pressure (pO₂) of >600 mm Hg.

There is currently a dearth of literature describing the results of treatment with the TherOx® AO system. Initial animal studies reported significant increases in distal arterial pO₂ in the AO treatment group compared to control animals (p<0.01) (Spears et al 1997b). A later study performed on dogs reported a significant increase in left ventricular ejection fraction (LVEF) in AO treated animals when compared to the control group (p<0.05) (Spears et al 2003).

Two studies were included for assessment in this report. The first human clinical pilot study (Intervention level IV evidence) reported on the use of TherOx® AO in 29 patients who had undergone percutaneous transluminal coronary angioplasty within 24 hours of AMI symptom onset (Dixon et al 2002). This study reported significant improvement in LVEF at one and three month follow-up (p<0.01) in addition to significant improvement in wall motion score indexes (WMSI) as early as 24 hours post-AO treatment (p<0.01).

One peer reviewed study and several abstracts reported on the progress of the AMIHOT randomised controlled trial (Intervention level II evidence). A total of 269 AMI patients, presenting within 24 hours of symptom onset, were randomised to either treatment with AO or standard treatment alone. Patients were follow-up for three months. Complete results of this trial have not been reported as yet.

The study by Warda et al (2005) reported the results of a subgroup of patients (n=50) within the AMIHOT trial, who had PCI followed by AO treatment within six hours of AMI symptom onset. Significant improvements were reported in LVEF from baseline to end of follow-up within the AO treated group (p<0.05) and between the AO and control groups (p<0.05). Abstracts reported a significant improvement in WMSI in the AO treated group when compared to the control group at three-month follow-up (p<0.01) (Martin et al 2004b). Greater improvements in WMSI were reported for the subgroup of patients who underwent treatment within six hours of symptom onset (p<0.01) (Martin et al 2005).
Mortality was reported in both of the peer reviewed papers, however these deaths were deemed to be not associated with the AO treatment protocol. There was one serious adverse event (3.4%), where the patient required a blood transfusion after excessive bleeding at the femoral access site for catheterisation.

In summary, the TherOx® AO system appears to be effective in increasing the left ventricular ejection fraction and decreasing the wall motion score index when compared to standard treatment alone, for patients presenting within 24 hours of AMI symptom onset. Both of these factors indicate improved left ventricular function. These improvements are greater for patients who are treated within six hours of AMI symptom onset. However, follow-up was short-term (3 months) in the studies included in this assessment. What the improvement in LVEF and WMSI mean for patient survival in the long term is unclear. It is also unclear from these studies what the effect of AO treatment would be for patients who present late with symptoms of AMI. In addition, the number of patients reported on in the two peer reviewed studies are quite small considering the large patient group that would be available for treatment of this kind (n=29 & 24 patients treated with AO). It would be prudent to await the complete results of the AMIHOT trial, which are expected in late 2005.

There are currently no cost-effectiveness data available for the utilisation of the TherOx® AO system. At this present moment in time there is no evidence to suggest that treatment with AO reduces the amount of time spent in hospital after AMI. However, treatment with AO may reduce the extent of LV injury, the number of re-infarctions or recurrent ischaemia, and in so doing may reduce the overall costs of AMI on the health system.
## Appendix A: Levels of Evidence

<table>
<thead>
<tr>
<th>Level</th>
<th>Intervention</th>
<th>Diagnosis</th>
<th>Prognosis</th>
<th>Aetiology</th>
<th>Screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>I*</td>
<td>A systematic review of level II studies</td>
<td>A systematic review of level II studies</td>
<td>A systematic review of level II studies</td>
<td>A systematic review of level II studies</td>
<td>A systematic review of level II studies</td>
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<tr>
<td>II</td>
<td>A randomised controlled trial</td>
<td>A study of test accuracy with: an independent, blinded comparison with a valid reference standard, §§ among consecutive patients with a defined clinical presentation ††</td>
<td>A prospective cohort study †*</td>
<td>A prospective cohort study</td>
<td>A randomised controlled trial</td>
</tr>
<tr>
<td>III-1</td>
<td>A pseudorandomised controlled trial (i.e. alternate allocation or some other method)</td>
<td>A study of test accuracy with: an independent, blinded comparison with a valid reference standard, §§ among non-consecutive patients with a defined clinical presentation ††</td>
<td>All or none §§§</td>
<td>All or none §§§</td>
<td>A pseudorandomised controlled trial (i.e. alternate allocation or some other method)</td>
</tr>
<tr>
<td>III-2</td>
<td>A comparative study with concurrent controls: Non-randomised, experimental trial † Cohort study Case-control study Interrupted time series with a control group</td>
<td>A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence</td>
<td>Analysis of prognostic factors amongst untreated control patients in a randomised controlled trial</td>
<td>A retrospective cohort study</td>
<td>A comparative study with concurrent controls: Non-randomised, experimental trial Cohort study Case-control study</td>
</tr>
<tr>
<td>III-3</td>
<td>A comparative study without concurrent controls: Historical control study Two or more single arm study ‡ Interrupted time series without a parallel control group</td>
<td>Diagnostic case-control study ††</td>
<td>A retrospective cohort study</td>
<td>A case-control study</td>
<td>A comparative study without concurrent controls: Historical control study Two or more single arm study</td>
</tr>
<tr>
<td>IV</td>
<td>Case series with either post-test or pre-test/post-test outcomes</td>
<td>Study of diagnostic yield (no reference standard) ††</td>
<td>Case series, or cohort study of patients at different stages of disease</td>
<td>A cross-sectional study</td>
<td>Case series</td>
</tr>
</tbody>
</table>
**Tablenotes**

* A systematic review will only be assigned a level of evidence as high as the studies it contains, excepting where those studies are of level II evidence.

† Definitions of these study designs are provided on pages 7-8 How to use the evidence: assessment and application of scientific evidence (NHMRC 2000b).

‡ This also includes controlled before-and-after (pre-test/post-test) studies, as well as indirect comparisons (ie. utilise A vs B and B vs C, to determine A vs C).

§ Comparing single arm studies ie. case series from two studies.

** The dimensions of evidence apply only to studies of diagnostic accuracy. To assess the effectiveness of a diagnostic test there also needs to be a consideration of the impact of the test on patient management and health outcomes. See MSAC (2004) Guidelines for the assessment of diagnostic technologies. Available at: www.msac.gov.au.

§§ The validity of the reference standard should be determined in the context of the disease under review. Criteria for determining the validity of the reference standard should be pre-specified. This can include the choice of the reference standard(s) and its timing in relation to the index test. The validity of the reference standard can be determined through quality appraisal of the study. See Whiting P, Rutjes AWS, Reitsma JB, Bossuyt PMM, Kleijnen J. The development of QADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. BMC Medical Research Methodology, 2003, 3: 25.

†† Well-designed population based case-control studies (eg population based screening studies where test accuracy is assessed on all cases, with a random sample of controls) do capture a population with a representative spectrum of disease and thus fulfill the requirements for a valid assembly of patients. These types of studies should be considered as Level II evidence. However, in some cases the population assembled is not representative of the use of the test in practice. In diagnostic case-control studies a selected sample of patients already known to have the disease are compared with a separate group of normal/healthy people known to be free of the disease. In this situation patients with borderline or mild expressions of the disease, and conditions mimicking the disease are excluded, which can lead to exaggeration of both sensitivity and specificity. This is called spectrum bias because the spectrum of study participants will not be representative of patients seen in practice.

‡‡ Studies of diagnostic yield provide the yield of diseased patients, as determined by an index test, without confirmation of accuracy by a reference standard. These may be the only alternative when there is no reliable reference standard.

*** At study inception the cohort is either non-diseased or all at the same stage of the disease.

§§§ All or none of the people with the risk factor(s) experience the outcome. For example, no smallpox develops in the absence of the specific virus; and clear proof of the causal link has come from the disappearance of smallpox after large-scale vaccination.

††† If it is possible and/or ethical to determine a causal relationship using experimental evidence, then the ‘Intervention’ hierarchy of evidence should be utilised. If it is only possible and/or ethical to determine a causal relationship using observational evidence (ie. cannot allocate groups to a potential harmful exposure, such as nuclear radiation), then the ‘Aetiology’ hierarchy of evidence should be utilised.

Note 1: Assessment of comparative harms/safety should occur according to the hierarchy presented for each of the research questions, with the proviso that this assessment occurs within the context of the topic being assessed. Some harms are rare and cannot feasibly be captured within randomised controlled trials; physical harms and psychological harms may need to be addressed by different study designs; harms from diagnostic testing include the likelihood of false positive and false negative results; harms from screening include the likelihood of false alarm and false reassurance results.

Note 2: When a level of evidence is attributed in the text of a document, it should also be framed according to its corresponding research question eg. level II intervention evidence; level IV diagnostic evidence; level III-2 prognostic evidence etc.

Hierarchies adapted and modified from: NHMRC 1999; Lijmer et al 1999; Phillips et al 2001; Bandolier editorial 1999)
## Appendix B: Profiles of studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>Study design</th>
<th>Study population</th>
<th>Study details</th>
<th>Outcome assessed</th>
<th>Length of follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dixon, SR, Bartorelli, AL, Marcovitz, PA, Spears, R, David, S, Grinberg, I, Qureshi, MA, Pepi, M, Trabattoni, D, Fabbrocchi F, Montorsi, P, O'Neill, WW (2002)</td>
<td>Multicentre Michigan, USA, Milan, Italy</td>
<td>Case series Intervention level of evidence IV</td>
<td>29 patients with AMI, undergoing primary angioplasty within 24 hours from symptom onset. Mean age 58.9 ± 12.6 years</td>
<td>Inclusion criteria: chest pain &gt;30 mins, ST-segment elevation &gt;1mm in 2 limb leads or &gt;2mm in precordial leads. Exclusion criteria: cardiogenic shock, need for intra-aortic balloon pump before or during coronary angioplasty, significant left main disease, use of a non-balloon or stent device, TIMI flow grade &lt;2 after intervention, CABG within 1 month, severe cardiac valvular stenosis or insufficiency, pericardial disease, non-ischaemic cardiomyopathy and pregnant women. AO infusion for 60-90 mins</td>
<td>Primary endpoints: clinical, electrical, haemodynamic instability during AO infusion, death, bleeding, recurrent ischaemia, target vessel revascularisation and new or progressive heart failure Clinical: chest pain, ST elevation, abnormal flow in the infarcted related artery Electrical: heart block, ventricular arrhythmia Haemodynamic: changes in heart rate, systemic or pulmonary artery pressures</td>
<td>Clinical 30 days, functional 3 months</td>
</tr>
<tr>
<td>Warda, HM, Bax, JJ, Bosch, JG, Atsma, DE, Jukema, JW, van der Wall, EE, van der Laarse, A, Schalij, MJ, Oemrawsingh, PV (2005)</td>
<td>Multicentre Leiden, Netherlands, Alexandria, Egypt</td>
<td>RCT Intervention level of evidence II</td>
<td>50 patients with AMI (anterior) underwent PCI within 6 hours from symptom onset, randomised to standard care (n=26, mean age 59 ± 12 years) or</td>
<td>Exclusion criteria: severe obstructive pulmonary disease, recent CABG, cardiogenic shock, intra-aortic balloon pump before or during PCI, proximal stenosis that impeded delivery of AO.</td>
<td>Left ventricular ejection fraction and left ventricular remodelling</td>
<td>24 hours and 30 days</td>
</tr>
<tr>
<td>Study Description</td>
<td>Intervention Group</td>
<td>Results</td>
<td>Location/Global Details</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------------------------------------------------------------------------</td>
<td>--------------------</td>
<td>------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presented as an abstract to the Transcatheter Cardiovascular Therapeutics Conference, 2004 (Warda et al 2004)</td>
<td>AO intervention group (n=24, mean age 59 ± 14 years)</td>
<td>presence of a non-stented dissection after completion of the procedure, TIMI flow &lt;2 after PCI.</td>
<td>Michigan, USA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presenting authors: Martin, JL, Dixon, S, David, S, Pensyl, C, Lindsay, B, O'Neill, WW</td>
<td>RCT Intervention level of evidence II</td>
<td>Initial 20 patients with AMI undergoing PCI within 24 hours from symptom onset, randomised to standard care or AO intervention group</td>
<td>AMI HOT trial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study presented as an abstract to the American College of Cardiology 52nd Annual Scientific Session, 2003</td>
<td>Safety of AO procedure</td>
<td>Not stated</td>
<td>Multicentre Pennsylvania, USA Michigan, USA Leiden, Netherlands Milan, Italy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presenting authors: Martin, JL, Day, F, Dixon, S, David, S, Pensyl, C, Hermiller, J, Oemrawsingh, P, Bartorelli, A, O'Neill, WW</td>
<td>RCT Intervention level of evidence II</td>
<td>Initial 90 patients with AMI undergoing PCI within 24 hours from symptom onset, randomised to standard care or AO intervention group</td>
<td>AMI HOT trial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study presented as an abstract to the Transcatheter Cardiovascular Therapeutics Conference, 2003</td>
<td>Safety of AO procedure</td>
<td>Not stated</td>
<td>Multi-centre Pennsylvania, USA Michigan, USA Leiden, Netherlands Milan, Italy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Author(s)</td>
<td>Study Location</td>
<td>Study Type</td>
<td>Study Details</td>
<td>Outcome Measures</td>
<td>Study Duration</td>
<td></td>
</tr>
<tr>
<td>--------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------</td>
<td>-----------------</td>
<td>---------------------------------------------------------------------------------------------------------------</td>
<td>---------------------------</td>
<td>----------------------</td>
<td></td>
</tr>
<tr>
<td>Martin, JL, Day, F, Dixon, S, Atsma, D, Oemrawsingh, PV, Pensyl, C, Lindsay, B, Bartorelli, AL, O'Neill, WW</td>
<td>Mult-centre, Pennsylvania, USA, Michigan, USA, Leiden, Netherlands, Milan, Italy</td>
<td>RCT</td>
<td>Initial 200 patients with AMI undergoing PCI within 24 hours from symptom onset, randomised to standard care or AO intervention group</td>
<td>AMIHOT trial</td>
<td>Safety of AO procedure</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Not stated</td>
<td></td>
</tr>
<tr>
<td>Martin, JL, Lindsay, B, Oemrawsingh, PV, Atsma, D, Krukoff, MW, Dixon, S, Bartorelli, AL, O'Neill, WW</td>
<td>Mult-centre, Pennsylvania, USA, Michigan, USA, Leiden, Netherlands, Milan, Italy</td>
<td>RCT</td>
<td>269 patients with AMI undergoing PCI within 24 hours from symptom onset, randomised to standard care or AO intervention group</td>
<td>AMIHOT trial</td>
<td>Resolution of ST elevation, regional wall motion</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>24 hours, one and three months</td>
<td></td>
</tr>
<tr>
<td>Martin, JL, Oemrawsingh, PV, Bartorelli, AL, Dixon, SD, Krukoff, MW, Lindsay, BS, Atsma, DA, O'Neill, WW</td>
<td>Mult-centre, Pennsylvania, USA, Michigan, USA, Leiden, Netherlands, Milan, Italy</td>
<td>RCT</td>
<td>269 patients with AMI undergoing PCI within 24 hours from symptom onset, randomised to standard care or AO intervention group</td>
<td>AMIHOT trial</td>
<td>Resolution of ST elevation, regional wall motion</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>12 months</td>
<td></td>
</tr>
</tbody>
</table>

AO = aqueous oxygen, LV = left ventricular, CABG = coronary artery bypass graft, TIMI = thrombolysis in myocardial infarction, RCT = randomised controlled trial, PCI = percutaneous coronary intervention, AMIHOT = Acute Myocardial Infarction Hyperbaric Oxygen Treatment trial
Appendix C: Short- vs long-term follow-up

In summary, results indicate that the TherOx® AO system appears to be effective in increasing left ventricular ejection fraction and decreasing the wall motion score index when compared to standard treatment alone, for patients presenting within 24 hours of AMI symptom onset. This indicates improvement in left ventricular function. Patients who are treated within six hours of AMI symptom onset demonstrate even greater improvement in left ventricular function. Studies included in this assessment had short-term follow-up (3 months). Treatment with AO demonstrated short-term improvements in heart function following ischaemia; however what the improvement in LVEF and WMSI means for patient survival in the long term is unclear from these results.

There is a wealth of literature which describes the outcomes of a variety of treatment protocols for AMI (thrombolysis, percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG)) . Traditionally, the major outcome endpoints used in cardiac surgery have been the 30-day mortality and morbidity rates, and may also include length of hospital stay, resource utilisation and patient satisfaction. Intermediate patient outcomes measured at up to six months include morbidity and mortality rates, cardiac health status (functional status after treatment), health-related measures of quality of life, patient satisfaction and ability to work. Long-term outcome measurements include quality of life, patient satisfaction, and ability to work for a period of one year or longer after surgery (Kurki 2002).

A search was conducted for meta-analyses of randomised controlled trials which described longer-term outcomes (> 30 days) for patients who had undergone PCI within 24 hours of AMI symptom onset. The search was limited to treatment with PCI, as the treatment arms in the Therox® AO studies consisted of PCI followed by Therox® AO, or PCI alone. Few studies included in meta-analyses reported outcome measures beyond the 30-day cut off point. An updated meta-analysis by Hartwell et al (2005) reported long-term outcomes of PCI versus thrombolysis alone. Hartwell et al (2005) presented the results of the early studies separately to the meta-analysis of the current studies (Hartwell et al 2005). These results were not combined into a single pooled statistic (Table 1). The meta-analysis by Cucherat et al (2002) contained values that were found to be incorrect and has since been withdrawn and is in the process of being updated.
Table 8  Results of early studies

<table>
<thead>
<tr>
<th>Study</th>
<th>6-week mortality</th>
<th>6-month or 12-month mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cucherat et al (2002)</td>
<td>RR 0.68 [0.50, 0.95]</td>
<td>RR 1.27 [0.42, 3.89]</td>
</tr>
<tr>
<td></td>
<td>( \chi^2 2.99 ) OR 0.56 [0.33, 0.94]</td>
<td>( \chi^2 0.65 ) OR 0.91 [0.42, 2.00]</td>
</tr>
<tr>
<td></td>
<td>Z= 2.29 ARR 2.1%</td>
<td>Z= 0.42 ARR 0.4%</td>
</tr>
<tr>
<td></td>
<td>12-month mortality</td>
<td>12-month combined mortality or non-fatal reinfarction</td>
</tr>
<tr>
<td></td>
<td>OR 0.91 [0.42, 2.00]</td>
<td>OR 0.88 [0.45, 1.72]</td>
</tr>
<tr>
<td></td>
<td>ARR 1.0%</td>
<td>ARR 0.9%</td>
</tr>
</tbody>
</table>

RR = relative risk [95% CI] <1.0 favours PCI compared to thrombolysis alone, ARR = absolute risk reduction, df = degrees of freedom, OR = odds ratio <1.0 favours PCI compared to thrombolysis alone

The updated meta-analysis did not combine the results of the earlier studies as it was felt that an increase in stenting and the use of glycoprotein IIb/IIa inhibitors may improve the results of PCI. Long-term mortality was reported by nine studies for PCI versus different thrombolytic agents (Table 2).

Table 2  Results of meta-analysis

<table>
<thead>
<tr>
<th>Meta-analysis</th>
<th>Short-term mortality (6 weeks) (14 studies)</th>
<th>Meta-analysis</th>
<th>Long-term mortality (≥ 6 months) (9 studies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>Angioplasty 66/1761 Thrombolysis 135/1778</td>
<td>Total</td>
<td>Angioplasty 43/810 Thrombolysis 70/828</td>
</tr>
<tr>
<td>Test for heterogeneity</td>
<td>( \chi^2 = 13.19, df=13, p =0.43 )</td>
<td>Test for heterogeneity</td>
<td>( \chi^2 = 8.31, df=8, p =0.4 )</td>
</tr>
<tr>
<td>Test for overall effect</td>
<td>Z = -3.36, p = 0.0008</td>
<td>Test for overall effect</td>
<td>Z = -2.61, p = 0.009</td>
</tr>
<tr>
<td>RR_p = 0.64 [0.49, 0.83]</td>
<td>RR_p = 0.62 [0.43, 0.89]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

RR_p = pooled relative risk [95% CI], df= degrees of freedom

One study by Aversano et al (2002) reported data for long-term (6-months) outcome measures such as mortality, recurrent myocardial infarction, stroke and the need for a CABG procedure (Table 3).
Table 3

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcome measure</th>
<th>6 weeks PCI n (%)</th>
<th>Thromb n (%)</th>
<th>Diff</th>
<th>6 months PCI n (%)</th>
<th>Thromb n (%)</th>
<th>Diff</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aversano et al (2002)</td>
<td>Mortality</td>
<td>12 (5.3)</td>
<td>16 (7.1)</td>
<td>p=0.44</td>
<td>14 (6.2)</td>
<td>16 (7.1)</td>
<td>p=0.72</td>
</tr>
<tr>
<td></td>
<td>Recurrent MI</td>
<td>11 (4.9)</td>
<td>20 (8.8)</td>
<td>p=0.09</td>
<td>12 (5.3)</td>
<td>24 (10.6)</td>
<td>p=0.04</td>
</tr>
<tr>
<td></td>
<td>Stroke</td>
<td>3 (1.3)</td>
<td>8 (3.5)</td>
<td>p=0.13</td>
<td>5 (2.2)</td>
<td>9 (4.0)</td>
<td>p=0.28</td>
</tr>
<tr>
<td></td>
<td>CABG</td>
<td>28 (12.4)</td>
<td>42 (18.6)</td>
<td>p=0.07</td>
<td>30 (13.3)</td>
<td>44 (19.5)</td>
<td>p=0.08</td>
</tr>
<tr>
<td></td>
<td>Composite</td>
<td>24 (10.7)</td>
<td>40 (17.7)</td>
<td>p=0.03</td>
<td>28 (12.4)</td>
<td>45 (19.9)</td>
<td>p=0.03</td>
</tr>
<tr>
<td></td>
<td>endpoint: death, recurrent MI or stroke</td>
<td>OR 0.52 [0.30, 0.89]</td>
<td></td>
<td></td>
<td>OR 0.57 [0.34, 0.95]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

OR = odds ratio <1.0 favours PCI compared to thrombolysis alone, Thromb = thrombolysis, Diff = between group differences

In addition, a study by de Boer et al (2002) reported long-term outcomes measured at 12 and 24-months (Table 4).

Table 4

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcome measure</th>
<th>30-day PCI n (%)</th>
<th>Thromb n (%)</th>
<th>RR (thromb)</th>
<th>p=0.04</th>
<th>12-months PCI n (%)</th>
<th>Thromb n (%)</th>
<th>RR (thromb)</th>
<th>p=0.03</th>
<th>24-months PCI n (%)</th>
<th>Thromb n (%)</th>
<th>RR (thromb)</th>
<th>p=0.003</th>
</tr>
</thead>
<tbody>
<tr>
<td>de Boer et al (2002)</td>
<td>Mortality</td>
<td>3 (7.0)</td>
<td>9 (22.0)</td>
<td>4.0 [0.9, 24.6]</td>
<td>p=0.04</td>
<td>5 (11.0)</td>
<td>12 (29.0)</td>
<td>3.4 [1.0, 13.5]</td>
<td>p=0.03</td>
<td>7 (15)</td>
<td>13 (32.0)</td>
<td>2.5 [1.0, 6.2]</td>
<td>p=0.04</td>
</tr>
<tr>
<td></td>
<td>Composite</td>
<td>4 (9.0)</td>
<td>12 (29.0)</td>
<td>4.3 [1.2, 20.0]</td>
<td>p=0.01</td>
<td>6 (13.0)</td>
<td>18 (44.0)</td>
<td>5.2 [1.7, 18.1]</td>
<td>p=0.001</td>
<td>9 (20.0)</td>
<td>18 (44.0)</td>
<td>3.1 [1.4, 7.0]</td>
<td>p=0.003</td>
</tr>
<tr>
<td></td>
<td>endpoint: death, recurrent MI or stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
</tbody>
</table>

RR = relative risk [95% CI] <1.0 favours PCI compared to thrombolysis alone

Results appear to be mixed, with earlier studies indicating an increased risk of mortality at six months (OR= 0.91) when compared to six weeks (OR= 0.56) for patients treated with PCI when compared to thrombolysis (Michels and Yusef, 1995). Similar results were reported by Cucherat et al (2002), however these results have since been withdrawn. The meta-analysis by Michels and Yusef was conducted in 1995, and contains studies conducted in the 1980’s. Improvements in technique and materials since that time may explain the difference in results when compared to the updated meta-analysis. Later results indicate that there is no difference in the relative risk of mortality at six weeks compared to six months, when patients are treated with PCI compared to thrombolysis. The study by de Boer et al (2002) indicated a decrease in the relative risk of mortality at 12 and 24 months post-AMI for patients treated with PCI compared to thrombolysis alone.

Therefore, from these results, it would appear that a three month follow-up after treatment with Therox® AO is adequate.


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systematic review and economic evaluation', *Health Technol Assess*, 9 (17), 1-99, iii-iv.

Appendix D: HTA Internet Sites

AUSTRALIA
- Centre for Clinical Effectiveness, Monash University
- Health Economics Unit, Monash University
  http://chpe.buseco.monash.edu.au

AUSTRIA
- Institute of Technology Assessment / HTA unit
  http://www.oecaw.ac.at/ita/welcome.htm

CANADA
- Agence d’Evaluation des Technologies et des Modes d'Intervention en Santé (AETMIS)
  http://www.aetmis.gouv.qc.ca/en/?PHPSESSID=d8bc1dd748339249934305897bdc16f0
- Alberta Heritage Foundation for Medical Research (AHFMR)
  http://www.ahfmr.ab.ca/publications.html
- Canadian Coordinating Office for Health Technology Assessment (CCHOTA)
  http://www.ccohta.ca/entry_e.html
- Canadian Health Economics Research Association (CHERA/ACRES) – Cabot database
  http://www.mycabot.ca
- Centre for Health Economics and Policy Analysis (CHEPA), McMaster University
  http://www.chepa.org
- Centre for Health Services and Policy Research (CHSPR), University of British Columbia
  http://www.chspr.ubc.ca
- Health Utilities Index (HUI)
  http://www.fhs.mcmaster.ca/hug/index.htm
- Institute for Clinical and Evaluative Studies (ICES)
  http://www.ices.on.ca

DENMARK
- Danish Institute for Health Technology Assessment (DIHTA)
  http://www.dlihta.dk/publikationer/index_uk.asp
• Danish Institute for Health Services Research (DSI) 
  http://www.dsi.dk/engelsk.html

FINLAND
• FINOHTA  http://www.stakes.fi/finohta/e/

FRANCE
• L’Agence Nationale d’Accréditation et d’Evaluation en Santé (ANAES) 
  http://www.anaes.fr/

GERMANY
• German Institute for Medical Documentation and Information (DIMDI) / 
  HTA  http://www.dimdi.de/dynamic/en/

THE NETHERLANDS
• Health Council of the Netherlands Gezondheidsraad 
  http://www.gr.nl/adviezen.php

NEW ZEALAND
• New Zealand Health Technology Assessment (NZHTA) 
  http://nzhta.chmeds.ac.nz/

NORWAY
• Norwegian Centre for Health Technology Assessment (SMM) 
  http://www.oslo.sintef.no/smm/Publications/Engsmdrag/FrameSetPublications.htm

SPAIN
• Agencia de Evaluación de Tecnologías Sanitarias, Instituto de Salud “Carlos III”/Health Technology Assessment Agency (AETS) 
  http://www.isciii.es/acts/
• Catalan Agency for Health Technology Assessment  (CAHTA) 
  http://www.aatm.es/cgi-bin/frame.pl/ang/pu.html

SWEDEN
• Swedish Council on Technology Assessment in Health Care (SBU) 
  http://www.sbu.se/www/index.asp
• Center for Medical Health Technology Assessment
  http://www.cmt.liu.se/English/Engstartsida.html

SWITZERLAND
• Swiss Network on Health Technology Assessment (SNHTA)
  http://www.snhta.ch/

UNITED KINGDOM
• Health Technology Board for Scotland
  http://www.htbs.org.uk/Default.htm

• National Health Service Health Technology Assessment (UK) / National
  Coordinating Centre for Health Technology Assessment (NCCHTA)
  http://www.hta.nhsweb.nhs.uk/

• University of York NHS Centre for Reviews and Dissemination (NHS CRD)
  http://www.york.ac.uk/inst/crd/

• National Institute for Clinical Excellence (NICE)
  http://www.nice.org.uk/

UNITED STATES
• Agency for Healthcare Research and Quality (AHRQ)
  http://www.ahrq.gov/clinic/techix.htm

• Harvard School of Public Health – Cost-Utility Analysis Registry
  http://www.hsph.harvard.edu/cearegistry/

• U.S. Blue Cross/ Blue Shield Association Technology Evaluation Center
  (TEC) http://www.bcbs.com/tec/index.html


Klabunde, R. E. (2005). *Cardiovascular Physiology Concepts* [Internet].


NHMRC (1999). A guide to the development, implementation and evaluation of clinical practice guidelines, National Health and Medical Research Council, Commonwealth of Australia, Canberra, ACT.


