

DICE Investigators

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DICE (Dextran In Carotid Endarterectomy)

A Multicentre, Randomised, Placebo-controlled trial of intravenous 10% Dextran 40 (Rheomacrodex), in the Prevention of Stroke in Carotid Surgery.

PROTOCOL
Confidential



**Coordinating centres
JHH & NSRI**



TRIAL ADMINISTRATIVE STRUCTURE



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Dextran in Carotid Endarterectomy (DICE) Trial - A randomised, controlled trial of 10% dextran 40 (Rheomacrodex) in the prevention of stroke complicating carotid endarterectomy.*Hypothesis & Aim*

That the administration of 10% dextran 40 during and after Carotid Endarterectomy (CEA) will reduce the risk of ipsilateral fatal and non-fatal stroke by 50% or more within the first 30 postoperative days. We aim to test this hypothesis by evaluating the clinical outcome at 30 days postoperatively in patients with carotid atherosclerosis undergoing endarterectomy randomised to receive either a 10% dextran 40 or placebo infusion perioperatively.

Background

Thromboembolism reportedly accounts for between 38% (Riles et al, 1994) and 68% (Krul et al, 1989) of strokes complicating carotid endarterectomy. The use of antiplatelet agents may reduce this risk of stroke in CEA. Low molecular weight dextrans have a number of circulatory effects of theoretical benefit in the vascular surgical setting and may reduce the risk of clinically significant carotid artery thrombosis. However, the efficacy of dextrans in the prevention of ischaemic stroke in CEA has not been evaluated in a formal clinical trial.

Research Plan

This is a multi-centre, randomised, double blind, placebo-controlled therapeutic trial. The trial is administered by a steering committee and overseen by a safety & efficacy monitoring committee. 1412 patients undergoing CEA will be recruited.

Inclusion and Exclusion Criteria

Patients with symptomatic and asymptomatic carotid atherosclerotic plaque considered suitable for CEA are eligible for inclusion. The patient must be capable of giving a written informed consent. Patients are excluded if they have a documented history of congestive cardiac failure (NYHA \geq grade 3), unstable angina or acute myocardial infarction within 3 months of surgery; renal impairment as measured by a serum creatinine of greater than 0.20 mmol/l; thrombocytopenia of less than 100,000/mm³; post-radiotherapy stenosis; previous hypersensitivity to dextrans, patients who have received dextrans or other haemodilution therapies over the preceding 72 hours, combined CEA/CABGs procedure or concomitant ipsilateral balloon and/or stenting procedure with CEA. Patients remaining on warfarin during surgery **and** those who will receive concomitant heparin therapy post-operatively are also excluded. Patients who are treated with warfarin (without heparin) may be included if the INR on the day of surgery is below 1.5.

Trial therapy

Therapy is commenced at induction of anaesthesia and consists of an initial bolus of 20 ml of dextran 1 ("promit") or normal saline given intravenously followed by intravenous infusion of 10% dextran 40 or normal saline placebo at an infusion rate of 125 ml/hour for 4 hours then 42 ml/hour for a further 12 hours. Operative techniques, anaesthesia and intra-operative medication are at the discretion of the attending surgeon and anaesthetist. The use of aspirin or other antiplatelet therapy perioperatively is also at the discretion of the attending clinician. Commencement of therapeutic anticoagulation during the first 30 postoperative days is documented.

All patients undergo a full clinical neurological examination by a study neurologist preoperatively, immediately after surgery, and at 24 hours and 30 days postoperatively. Pre and post-operative neurological impairment is measured using the NIH Stroke Scale. Pre and post-operative handicap is measured using the Modified Rankin Score. In the interval between hospital discharge and the 30-day follow-up, patients are provided with a card outlining cerebral ischaemic symptoms and are instructed to contact the study investigators in the event of such symptoms. It is recommended that management of cerebral ischaemia be along the lines of standard clinical management with exclusion of intracranial haemorrhage by CT scanning as soon as possible but within 2 weeks from ictus allowing definition of stroke mechanism and topography.

Outcomes

Primary endpoint

- Ipsilateral fatal and non-fatal stroke, hemispheric or retinal, within 30 days of carotid endarterectomy.

Secondary endpoints

- Any non-fatal or fatal stroke within 30 days of carotid endarterectomy.
- Death due to any cause within 30 days of carotid endarterectomy.
- Ipsilateral TIA.

Sample size

In order to detect a risk reduction in the treatment group of 50% (OR 0.5), assuming a primary endpoint rate of 6% in the placebo group at an alpha set at 0.05 (2 tailed) and a power of 80%, 706 patients in total will be required in each group.

Safety & efficacy monitoring

At Feb 2002, the primary outcome event rate is 9.4% (40 primary outcome events), considerably above the 6% envisaged *a priori* but statistically consistent with the stroke and death rate estimate of 7.7% (95%CI 5.0-10.2) from a systematic review of neurological audits of CEA morbidity and mortality (Rothwell et al, 1996). A continuing primary outcome event rate in excess of 6% will conceivably increase the power of the study. Predefined rules call for the Safety Monitoring Committee to review the primary outcome rates between the two treatment groups if there is a sustained outcome event rate greater than 10%. The Safety and Efficacy Monitoring Committee have reviewed adverse events for the initial 350 patients recruited and have expressed no concerns. The rates of wound haematoma are consistent with those observed in the ACE trial and also those observed in the NSW Audit of Carotid Endarterectomy (Middleton et al 2002). An interim analysis is planned when two thirds of the expected primary outcomes events are accrued (56 events) with stopping rules defined by the Fleming-O'Brien boundary.

Dextran in Carotid Endarterectomy (DICE) Trial - A randomised, controlled trial of 10% dextran 40 (Rheomacrodex) in the prevention of stroke complicating carotid endarterectomy.

Trial Rationale

Carotid atherosclerosis and carotid endarterectomy:

The prevalence of >50% carotid artery stenosis increases with increasing age and is about 0.5% for age group 50-54 increasing to 8% for age ≥ 75 (NHMRC Clinical Practice Guidelines 1996). Using Australian Bureau of Statistics estimates, there are about 150,000 Australians over the age of 50 with significant carotid stenosis. Atherosclerotic carotid artery stenosis is conservatively estimated to cause at least 20% of strokes and thereby contributes significantly to the overall burden of stroke.

Carotid endarterectomy (CEA) provides a clear advantage for patients with severe carotid stenosis who present with amaurosis fugax, transient ischaemic attack, or non-disabling stroke. Two large randomised multicentre trials, the North American Symptomatic Carotid Endarterectomy Trial (NASCET, North American Symptomatic Carotid Endarterectomy Trial Collaborators, 1991) and the European Carotid Surgery Trial (ECST, European Carotid Surgery Trialists' Collaborative Group, 1991) published almost simultaneously, have demonstrated efficacy in patients with severe carotid stenosis. In NASCET, there was an absolute risk reduction from CEA of 16.5%, relative risk reduction of 51% and number needed-to-treat of 8. After the first 30 post-operative days, the ipsilateral stroke rate in the surgical group was 5.5%. ECST revealed similar efficacy findings for symptomatic severe carotid stenosis, however the perioperative stroke and death rates were marginally higher with 7.5% having had a stroke or died within 30 days of surgery. In the more recently published 30-69% stenosis category, patients in ECST showed a trend toward poorer outcomes when treated surgically with any potential benefits being outweighed by perioperative stroke risk (European Carotid Surgery Trialists' Collaborative Group, 1998). However, the major stroke or death rate of 7.9% was relatively high compared to the results in the higher grade ECST and NASCET subsets. In NASCET, patients with <50% stenosis showed no significant benefit from surgery. Patients in the 50-69% category however, did show a modest benefit from CEA with a relative risk reduction of 29% ($P=0.045$). This risk reduction equates to the 'need-to-operate' on 15 patients to prevent 1 stroke over 5 years. The cost-effectiveness of operating on this group of patients is, therefore, questionable.

For asymptomatic patients the benefits of CEA are less certain and cost-effectiveness is comparatively poorer (NHMRC Clinical Practice Guidelines, 1996). The Asymptomatic Carotid Atherosclerosis Study (Executive Committee for the Asymptomatic Carotid Atherosclerosis Study, 1995) showed for the primary endpoint of ipsilateral stroke or perioperative stroke or death, an estimated 5-year event rate of 11.0% in the medical group compared with 5.1% in the surgical group. This gave an overall risk reduction of 53% (95% CI 22-72%) in favour of CEA. This equates to a number needed-to-treat of 17. Meta-analysis of all asymptomatic CEA trials reveals a trend favouring CEA, which does not reach statistical significance for the endpoint stroke or death (RR 0.83, 95% CI 0.67-1.02). Despite this, CEA for asymptomatic carotid stenosis is being enthusiastically embraced in some centres.

Since 1991, following the publication of the interim results of the two large randomised trials in symptomatic stenosis, the number of patients undergoing CEA in Australia has increased at a rate of between 10-15% per year (NHMRC Clinical Practice Guidelines 1996). In the US, it is estimated that 35-40,000 CEAs are performed annually (Easton, 1994). In Australia in 1994/5, an estimated 5,427 CEAs were performed (NHMRC Clinical Practice Guidelines, 1996). The modest, but statistically significant benefits in favour of CEA in the Asymptomatic Carotid Atherosclerosis Study published in 1995 and the 50-69% stenosis group in NASCET published in 1998 (North

American Symptomatic Carotid Endarterectomy Trial Collaborators, 1998), are likely to further increase the numbers of patients being offered CEA for stroke prevention. A major concern however, is that even in the best of surgical hands (as when CEA is performed in selected centres such as those recruiting into international multicentre trials), the operation carries a risk of stroke or death of 5-6%. Perioperative morbidity and mortality rates above these levels can jeopardise any net benefit the patient can hope to obtain from surgery. This is particularly so in the patients at lower risk with medical therapy alone, such as the asymptomatic group. A recent overview of published CEA morbidity and mortality results revealed perioperative stroke and death rates of up to 10% (Rothwell & Warlow, 1995), so high as to jeopardise efficacy of the procedure in any patient group.

Because CEA is being increasingly utilised and because the operation has a relatively narrow harm-benefit margin, strategies proven effective in reducing perioperative morbidity and mortality are urgently required. As stroke is the major cause of morbidity and mortality, antithrombotic therapies require proper investigation. To date, no such studies have been undertaken. This interventional study aims to test a therapeutic strategy that may reduce the risk of stroke from CEA. A positive outcome will improve the stroke risk reduction achieved by CEA and improve the cost-effectiveness of surgery.

The pathogenesis of cerebral ischaemia associated with carotid endarterectomy:

Stroke is the major potential complication of CEA. A recent meta-analysis of prospective neurological audits of complications of CEA demonstrates a stroke and death rate of 7-8% (Rothwell & Warlow, 1995). It is estimated that thromboembolism accounts for between 38% (Riles et al, 1994) and 68% (Krul et al, 1989) of perioperative ischaemic events and is the single most frequent cause of stroke in this setting. In the largest series examined (3062 endarterectomies over 26 years) 48% of thromboembolic ischaemic events occurred in the recovery room (Krul et al, 1989) suggesting an acute thromboembolic pathogenesis. From this series it was inferred that technical imperfection is the underlying cause of this phenomenon. In some cases however, carotid thrombosis was also recognised to occur following technically perfect operations. The usual operative finding noted at re-exploration was platelet and fibrin deposition at the endarterectomy site (Riles et al, 1994). Such platelet-fibrin deposition would be expected to result in downstream shedding of emboli.

Transcranial Doppler embolus detection provides a unique means of investigating cerebral ischaemia during CEA. Microemboli passing through the basal cerebral arteries produce high intensity transient signals (embolic signals) when those vessels are monitored with transcranial Doppler (TCD) (Russell, 1992; Casty, 1994; Markus & Harrison, 1995). The technique of Doppler microembolus detection has been validated in experimental model systems (Russell et al, 1991; Markus, 1995; Markus & Tegeler, 1995; Levi et al, 1996) and TCD detected cerebral microemboli have been noted in various clinical settings of high stroke risk (Gerraty et al, 1996; Infeld et al, 1996; Georgiadis et al, 1994; Siebler et al, 1993; Markus et al, 1994) including CEA (Padayachee et al, 1987; Spencer et al, 1990; Gaunt et al, 1994a; Gavrilescu et al, 1995).

Microembolus detection studies during CEA have reported an association between high numbers of embolic signals and the development of clinical, radiological and neuropsychological evidence of ischaemic damage in the territory of the insonated middle cerebral artery. Spencer et al, (1990) reported that frequent embolic signals were associated with the development of cerebral infarction in the insonated vessel territory in 2 of 63 patients monitored immediately postoperatively. In a series of 123 consecutive CEAs monitored intra-operatively, (Jansen et al, 1994), embolic signal counts exceeding 10 during arterial dissection or carotid clamp release were noted in 4 of 40 patients who were studied with pre- and post-operative magnetic resonance brain imaging. All 4 of

these patients showed the development of new clinically silent ischaemic lesions in the ipsilateral hemisphere. Gaunt et al, (1994a) noted that greater than 10 embolic signals detected during the arterial dissection phase of surgery was significantly associated with post-operative neuropsychological impairment and also reported isolated cases where frequent early post-operative micro embolic signals were indicative of incipient carotid thrombosis and heralded ischaemic stroke (Gaunt et al, 1994b).

Australian study of the natural history cerebral microembolism following carotid endarterectomy: Using a novel method of Doppler spectrum plus high-speed macro video image co-registration, Levi et al (1996) validated their transcranial Doppler instrument. The sensitivity and specificity of the instrument in the detection of particulate microemboli was assessed against the “gold standard” of the optical image of the embolus, which demonstrated a detection specificity of 100% and a detection sensitivity of 89% for particulate microemboli. Subsequently, inter-observer agreement in the counting of embolic signals was compared between nine international “benchmark” centres (including ARMC) using a standard recording of 2 hours of Doppler signal containing a variety of true positive embolic signals and artifacts. A high proportion of agreement (≥ 0.86) in embolic signal counting between centres was observed using accepted criteria and an embolic signal intensity threshold of 6 decibels or greater (Markus et al, 1997).

Levi et al (1997a) performed a systematic study of the natural history of microembolism detected downstream from the endarterectomy site in 65 patients undergoing CEA. Patients were studied at intervals out to 24 hours postoperatively with TCD insonation of the middle cerebral artery ipsilateral to the operation side. The initial 24 hours postoperatively is the highest risk period for cerebral ischaemia (Krul et al, 1989) and prior to this investigation, the occurrence of microemboli in this time period had not been thoroughly evaluated.

Study design was open and prospective with blinded off-line analysis of embolic signal counts at a 6-decibel threshold. End-points were any focal ischaemic neurological deficit and/or death out to 30 days postoperatively. Embolic signals were detected in 69% of cases during the first hour postoperatively with counts ranging from 0 to 212 per hour (mean 19/hr; SEM +/- 4.5; median 4/hr). In seven cases (10.8%), embolic signal counts were greater than 50 per hour. Five of these seven cases developed ischaemic neurological deficits in the territory of the insonated middle cerebral artery during the monitoring period (χ^2 45.9, $P < 0.001$). The positive predictive value of embolic signal counts greater than 50 per hour for cerebral ischaemia was 0.71.

The authors concluded that frequent embolic signals (greater than 50 per hour) in the early post-operative phase of CEA were predictive of ipsilateral focal cerebral ischaemia. These data support the findings of Spencer et al, (1990) and Gaunt et al, (1994b) that frequent microemboli in this setting can be pathogenic and are indicative of endarterectomy site thrombosis. Furthermore, there is potential for the use of embolus detection to guide such interventions as operative re-exploration or antithrombotic therapies.

Low molecular weight dextrans in carotid endarterectomy:

Dextrans are large polysaccharide polymers. The low molecular weight (40 Dalton) moieties have a number of circulatory effects, which includes haemodilution, reducing blood viscosity, reducing red cell aggregation and red cell rigidity along with antiplatelet effects (Weiss, 1967; Bergqvist, 1982; Ljungstrom, 1988; Nazzal et al, 1991). Dextrans have been shown to reduce platelet adhesion to vascular grafts (Christenson et al, 1988) and to improve the patency of lower limb arterial bypass grafts in a randomised controlled trial (Rutherford et al, 1984). The direct effect on platelet adhesiveness is probably mediated through an effect on the interaction between the von Willebrand factor and the platelet membrane (Aberg et al, 1979; Garrett et al, 1993). In a rabbit

microcirculation model, it has been demonstrated that dextrans affect the distribution of platelets in the vessel lumen causing them to concentrate in the central lumen and move away from the arteriolar wall (Woldhuis et al, 1993). This process may relate to alteration in capillary endothelium surface charges (Baldwin et al, 1991), and may be important in avoiding platelet contact with the thrombogenic surgically damaged vessel wall.

Antiplatelet agents may result in a reduction in the rate of ischaemic stroke during carotid surgery (Edwards et al, 1985) however, there have been no prospective randomised controlled trials conducted to examine this issue. Furthermore, prior to undertaking the studies outlined in the next few pages, there were no published data on the effects of low molecular weight dextrans on the incidence of brain embolism in the perioperative phase of CEA. Recently however Lennard et al, (1997) conducted an open, non-randomised study in which patients with frequent early post-operative microembolism were given dextran 40. In 7 patients treated openly, they noted a rapid reduction in rates of microembolism. Although suggestive of a beneficial effect on microembolism, these results require testing in a randomised controlled trial.

Prevention of microembolism following carotid endarterectomy: a randomised, double blind, placebo-controlled trial:

The objective of this study was to test the hypothesis that the administration of 10% dextran 40 during and after carotid endarterectomy would reduce the occurrence of cerebral microembolism detected by transcranial Doppler ultrasound monitoring. Microembolism was considered to be a surrogate endpoint for antithrombotic drug efficacy with the intention being that a positive efficacy result would support the worth of proceeding to a large-scale clinical outcome trial. The study design was prospective, randomised, double blind, and placebo controlled.

148 patients undergoing CEA, who were also suitable for perioperative TCD monitoring were randomised to either infusions of 10% dextran 40 or normal saline placebo. All patients received standard perioperative aspirin and heparin therapy. The middle cerebral artery ipsilateral to the CEA was monitored for 30 minutes on the patients return to the recovery room. Microemboli were detected as embolic signals using a 6dB intensity threshold at off-line review. The primary endpoint was a halving of the median embolic signal counts in the post-operative phase. Differences in embolic signal counts between groups were analysed according to intention to treat using the Mann-Whitney U - Wilcoxon Rank Sum W test.

The quality of TCD recordings was satisfactory for off-line embolic signal analysis in 141 cases. Demographic and risk factor profiles of the 141 patients in the treatment and placebo groups were well balanced, with no significant differences between baseline characteristics.

The infusion of 10% dextran 40 resulted in a significant reduction in the embolic signal counts at the 0-1 hour post-operative period. The embolic signal counts were non-parametrically distributed. The median count in the treatment group was 0 embolic signals/hour (range 0-78/hour) and in the placebo group, 2 embolic signals/hour (range 0-118/hr) (Mann-Whitney U, Wilcoxon Rank Sum test, P=0.043). No adverse haemostatic or allergic reactions occurred in either 10% dextran 40 or placebo groups.

This study demonstrated that an intravenous infusion of 10% dextran 40 during and after CEA produces a significant reduction in ipsilateral middle cerebral artery embolic signals in the early post-operative period. The time epoch studied (the 0-1 hour post-operative interval) is pertinent to the potential clinical relevance of the result. The early post-operative period is associated with the highest risk of thromboembolic cerebral ischaemia and is the time at which both the perioperative embolic signal counts are highest (Levi et al, 1997a,b) and the time at which embolic signals have been associated with the occurrence of stroke and transient cerebral ischaemia (Levi et al, 1997a; Gaunt et al, 1994a; Spencer et al, 1990). Although a correlation may exist between reduction in microembolism and improved clinical outcomes in CEA, the efficacy of 10% dextran 40 in preventing clinically relevant ischaemic events remains to be proven. The effect of 10% dextran 40 on clinical outcomes is under evaluation in Phase II of this study. The detailed methodology is outlined on the following pages.

Trial hypothesis and specific aim:

The trial hypothesis to be tested is that the administration of 10% dextran 40 during and after carotid endarterectomy will reduce the occurrence of ipsilateral stroke and stroke related death within the first 30 post-operative days. The trial objective is to test this hypothesis in patients with carotid artery atherosclerotic stenosis undergoing carotid endarterectomy with an otherwise standard operative and therapeutic regimen.

Trial Design:

The trial is a multi-centre, randomised, double blind, placebo-controlled trial of 10% dextran 40 in the peri-operative phase of CEA. Efficacy of 10% dextran 40 in the reduction of ipsilateral stroke and stroke related death will be assessed by randomly assigning patients to receive either 10% dextran 40 or normal saline commenced intra-operatively and continued over the next 16 hours. Clinical assessments by a study neurologist are performed pre-operatively, on arrival in the recovery room, at 24 hours postoperatively with a final clinical assessment performed at 30 days postoperatively blind to treatment allocation. The primary endpoint is ipsilateral fatal or non-fatal stroke. The sample size of 814 in each group will allow the detection of a 50% reduction in primary outcome event rates in the treatment group.

The trial coordinating centre, centralised database and data management centre is at the National Stroke Research Institute, Austin & Repatriation Medical Centre, Melbourne. Steering committee composition is outlined on page 2 of this brochure and will be expanded as additional centres enter the trial. The chairman of the Steering Committee is Dr Chris Levi. The Safety & Efficacy Monitoring committee comprises Dr Judith Frayne, Professor John McNeil, and Dr Richard Gerraty. The trial biostatistician is Dr John Wlodarczyk. Steering Committee teleconferences will be scheduled to occur following recruitment of each set of 100 patients and face-to-face meetings will be scheduled annually. The trial randomisation centre will be based at the Austin & Repatriation Medical centre. See Figure 1.

Patients:

All patients undergo a standard pre-operative work-up by the attending neurovascular teams including clinical assessment, full blood count, biochemical profile, electrocardiogram and chest X-ray. The trial neurologist and/or vascular surgeon at each recruiting centre confirms each patient's suitability on the basis of the defined Inclusion & Exclusion Criteria, and will obtain informed consent.

Censorship:

Patients are censored from the date of the primary endpoint, including all death, from the date of any cranial surgery and/or lost to follow-up.

Inclusion Criteria:

- Symptomatic or asymptomatic carotid artery atherosclerosis considered suitable for CEA performed under either general or loco-regional anaesthesia.

Exclusion Criteria:

- Documented history of congestive cardiac failure (NYHA \geq GD 3), unstable angina or acute myocardial infarction within 3 months of surgery.
- Renal impairment as measured by a serum creatinine of greater than 0.20 mmol/l.
- Thrombocytopenia of less than 100,000/mm³.
- Previous hypersensitivity to dextrans.
- Concomitant ipsilateral balloon and/or stenting procedure with CEA.
- Patients remaining on warfarin during surgery **and** those who will receive concomitant heparin therapy post-operatively are also excluded. Patients who are treated with warfarin (without heparin) may be included if the INR on the day of surgery is below 1.5.
- Lack of informed consent.
- Combined CEA/CABGs procedure
- Post radiotherapy stenosis

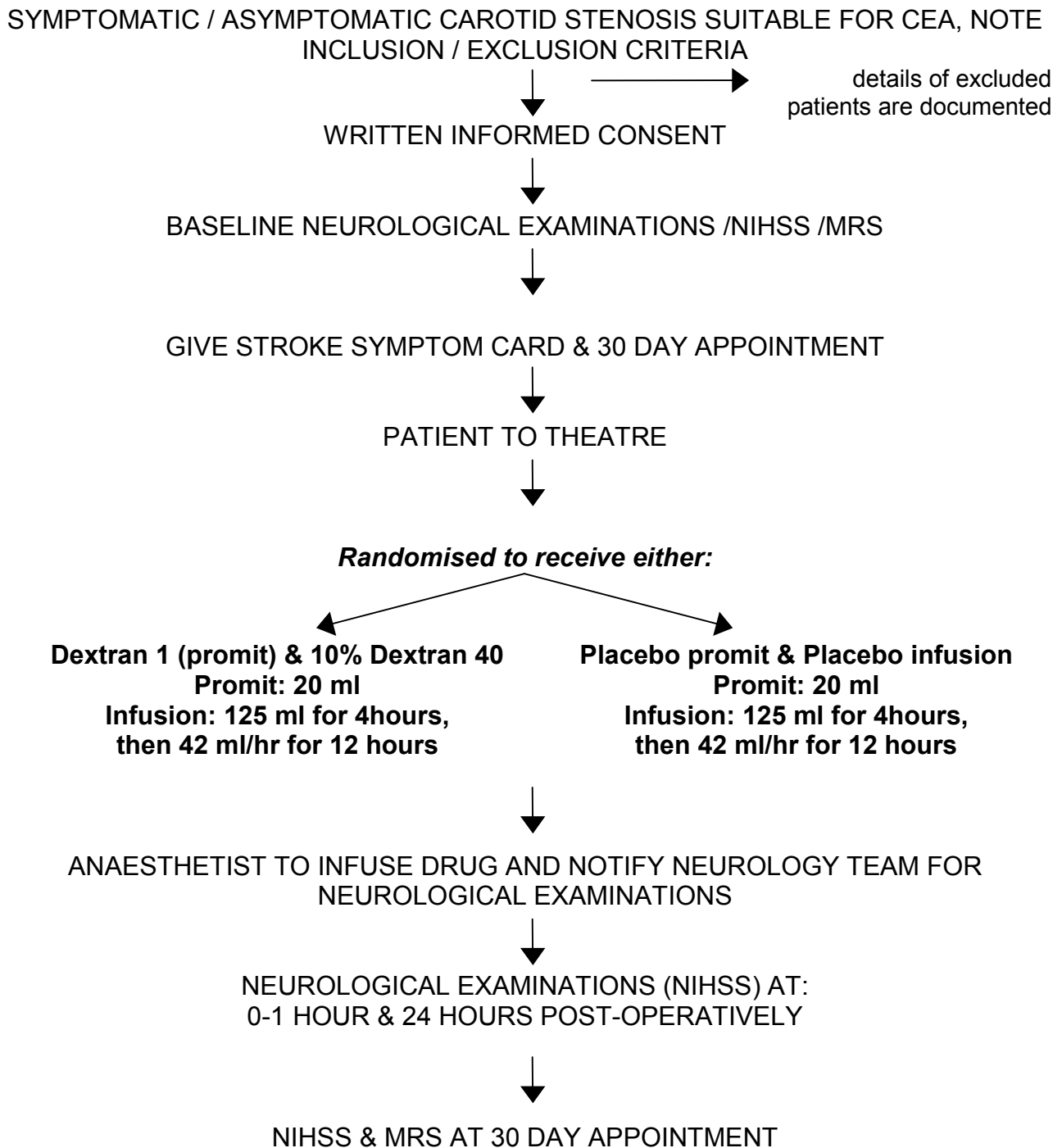


Figure 1. DICE Management Flow Chart

Baseline documentation:

Included in baseline documentation will be indication for CEA, diameter stenosis of the index carotid artery (duplex ultrasound and/or X-ray angiography) prior cerebrovascular events, cerebral CT or MRI scan results if available, clinical risk factor profile, medications, and status of the contralateral carotid artery as measured on duplex ultrasound and/or X-ray angiography.

SCHEDULE OF ASSESSMENTS

BASELINE NEUROLOGICAL EXAMINATIONS /NIHSS /mRS



NEUROLOGICAL EXAMINATIONS (NIHSS) AT:
0-1 HOUR & 24 HOURS POST-OPERATIVELY



NIHSS & mRS AT 30 DAY APPOINTMENT

Randomisation:

A central randomisation centre is currently located at the Austin & Repatriation Medical Centre Pharmacy Department. The Pharmacy Department at each centre will maintain an additional log of patient details and treatment allocation for purposes of cross checking or unblinding of patients in the event of a serious adverse outcome. Any patients who are randomised, but do not follow protocol for whatever reason, are still followed up by the intention-to-treat principle.

Trial therapy:

The active and placebo solutions are clear and colourless. The pre-medication will be loaded into generic 20ml syringes and active or placebo infusions will be loaded into 1,000 ml generic infusion bags. Both will be labeled with patient details and instructions for administration only. Therapy is prepared at the Pharmacy departments of the individual centres under laminar flow conditions. Therapy is required to be administered within 24 hours of preparation.

Therapy administration protocol:

Treatment consists of an initial bolus of 20 ml of dextran 1 ("promit") or normal saline placebo given intravenously at anaesthesia induction according to the guidelines suggested for prevention of hypersensitivity reactions. Intravenous infusion, given by volumetric infusion pump, of 10% dextran 40 in normal saline or normal saline placebo is then commenced immediately following premedication at an infusion rate of 125 ml/hour. After 4 hours the infusion rate is reduced to 42 ml/hour continuing for 12 hours. The infusion is then suspended, the total infusion time being 16 hours from the commencement of anaesthesia.

Concomitant antithrombotic medication:

Aspirin is continued at the discretion of the attending physicians and the use of intra-operative heparin and heparin reversal will be at the discretion of the attending surgeon and will be documented. Any need for commencement of therapeutic anticoagulation during the first 30 post-operative days is documented.

Operative technique:

No restriction on operative technique is imposed by the trial. In addition to recognised clinical predictors of outcome, the following operative variables are documented; general or loco-regional anaesthesia; intra-operative heparinisation; shunt placement; patch angioplasty; protamine use; outcome of intra-operative completion angiogram or duplex scan if performed; use of intra-operative monitoring with either stump pressures, TCD or EEG.

Sample size calculation:

Assuming a combined primary outcome measure rate of 6% in the placebo group (based on published meta-analysis figures (Rothwell & Warlow, 1995)), a 50% risk reduction would produce a 3% perioperative stroke and death rate in the treatment group. A 3% or lower perioperative stroke and death rate is that recommended for centres performing endarterectomy in the lower risk patients such as those with asymptomatic stenosis (Moore et al, 1995). In order to detect a risk reduction in the treatment group of 50% (OR 0.5), with an alpha set at 0.05 (2 sided) and a power of 80%, 706 patients are required in each group.

Data collection & analysis:

Data will be collected prospectively on standardised proformas and entered into a centralised database at the National Stroke Research Institute, Melbourne. Tracking of all patients and data will be the responsibility of the trial coordinator; data entry and “cleaning” will be the responsibility of the data manager. At Feb 2002, the primary outcome event rate is 9.4% (40 primary outcome events), considerably above the 6% envisaged *a priori* but statistically consistent with the stroke and death rate estimate of 7.7% (95%CI 5.0-10.2) from a systematic review of neurological audits of CEA morbidity and mortality (Rothwell et al, 1996). A continuing primary outcome event rate in excess of 6% will conceivably increase the power of the study. Predefined rules call for the Safety Monitoring Committee to review the primary outcome rates between the two treatment groups if there is a sustained outcome event rate greater than 10%. The Safety and Efficacy Monitoring Committee have reviewed adverse events for the initial 350 patients recruited and have expressed no concerns. The rates of wound haematoma are consistent with those observed in the ACE trial and also those observed in the NSW Audit of Carotid Endarterectomy (Middleton et al 2002). An interim analysis is planned when two thirds of the expected primary outcomes events are accrued (56 events) with stopping rules defined by the Fleming-O’Brien boundary.

Clinical neurological assessments:

All patients undergo a clinical neurological examination by the trial centre neurologist pre-operatively, on the patient returning to the recovery room, at 24 hours postoperatively and at 30 days postoperatively. Pre and post-operative neurological impairment is measured using the NIH Stroke Scale (NIHSS). Pre and post-operative handicap is measured using the Modified Rankin Score (MRS). In the interval between hospital discharge and the 30-day follow-up, patients are provided with a card outlining stroke symptoms and are instructed to contact the study investigators in the event of such symptoms.

Assessment of perioperative stroke, neurological impairment and handicap:

It is recommended that management of cerebral ischaemia be along the lines of standard clinical management with exclusion of intracranial haemorrhage by CT scanning. Patients having clinical stroke events undergo cerebral CT or MRI scanning within 2 weeks of the event, allowing definition of stroke mechanism and topography. The scanning will be read and documentation completed by the trial centre neurologist blind to treatment allocation. Strokes are defined as ischaemic, ischaemic with haemorrhagic transformation or primary haemorrhagic.

Stroke severity at 30 days is measured on the NIH Stroke Scale (NIHSS) and the Modified Rankin Score (mRS). NIHSS ≥ 14 is used to classify post-operative strokes as severe versus mild/moderate. If there is pre-existing impairment, an increase in NIHSS of ≥ 10 above baseline is classified as severe. Stroke handicap is classified as major if mRS is 3 to 5 or if mRS shows an increase in 2 or more from baseline. Minor strokes are classified as mRS 0 to 2 or an increase in score by 1 from baseline.

Blinding issues:

All clinical assessments are performed blind to treatment allocation. In the event of a serious adverse event possibly related to trial medication, the clinician may request unblinding of treatment allocation. In this event, the patient will continue in follow-up and be assessed at 30 days by an alternative neurologist blinded to the preceding events. These patients will be included in the primary efficacy analysis according to intention-to-treat principles.

Outcome measures:

Primary endpoint

- Ipsilateral fatal or non-fatal stroke, hemispheric or retinal, within 30 days of carotid endarterectomy.

Secondary endpoints

- Any non-fatal or fatal stroke within 30 days of carotid endarterectomy.
- Death due to any cause within 30 days of carotid endarterectomy.
- Ipsilateral TIA.

Monitoring for adverse events:

The following are monitored and documented at 30 days: any death considered by the site investigator to be potentially linked to trial medication; allergic reactions defined as either angioedema or anaphylaxis; acute post-operative cardiac failure requiring urgent treatment during the hospital stay; unstable angina, wound bleeding or haematoma; gastrointestinal or other mucocutaneous bleeding events, hyperperfusion syndrome not causing a stroke

Safety & Efficacy Monitor:

The independent safety and efficacy monitoring committee has reviewed the primary and secondary outcome measure rates and all other adverse events in the treatment groups for the first 250 patients (28 percent of the total expected primary events were in this analysis). The monitoring committee will assess outcome rates and adverse events in each of the treatment groups after 60% (44 strokes), and 80% (58 strokes) of the patients have been recruited as well as a final analysis after recruitment of all patients. The monitoring committee will advise the Steering Committee to stop recruitment in the event of a sustained and significant difference in outcome measures between treatment groups based on a Fleming & O'Brien boundary. In the event of such advice, recruitment will be suspended and the Steering Committee meeting will review the blinded outcome data and obtain advice from each of the regional Institutional Ethics Committees. A final decision on continuation or discontinuation will then be made.

Management of cerebral ischaemia:

It is recommended that management of cerebral ischaemia be along the lines of standard clinical management with exclusion of intracranial haemorrhage by CT scanning. Although it remains at the investigator's discretion, unblinding of patients who develop clinical features of cerebral ischaemia is discouraged. The senior investigator at each site should be consulted preferably before any unblinding occurs. Administration of antithrombotics should follow clinical need. Unblinding of the treatment allocation is discouraged.

DEFINITIONS:

- Ipsilateral stroke = acute onset of new focal neurological disturbance ipsilateral to the side of CEA and lasting ≥ 24 hours from onset.
- Any stroke = acute onset of new focal neurological disturbance with neurological signs lasting ≥ 24 hours.
- Ischaemic stroke = acute onset of new focal neurological disturbance lasting ≥ 24 hours from onset with CT or MRI scan exclusion of primary haemorrhage.
- Primary haemorrhagic stroke = acute onset of new focal neurological disturbance lasting ≥ 24 hours from onset with CT or MRI scan confirmation of primary haemorrhage.
- Hyper-perfusion syndrome = Ipsilateral headache, seizures & Intracerebral haemorrhage.

NEW YORK HEART ASSOCIATION FUNCTIONAL CLASSIFICATION*

CLASS	FUNCTIONAL CLASSIFICATION
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation dyspnea, or anginal pain.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation dyspnea, or anginal pain.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation dyspnea, or anginal pain.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

The criteria Committee of the New York Heart Association, 1964

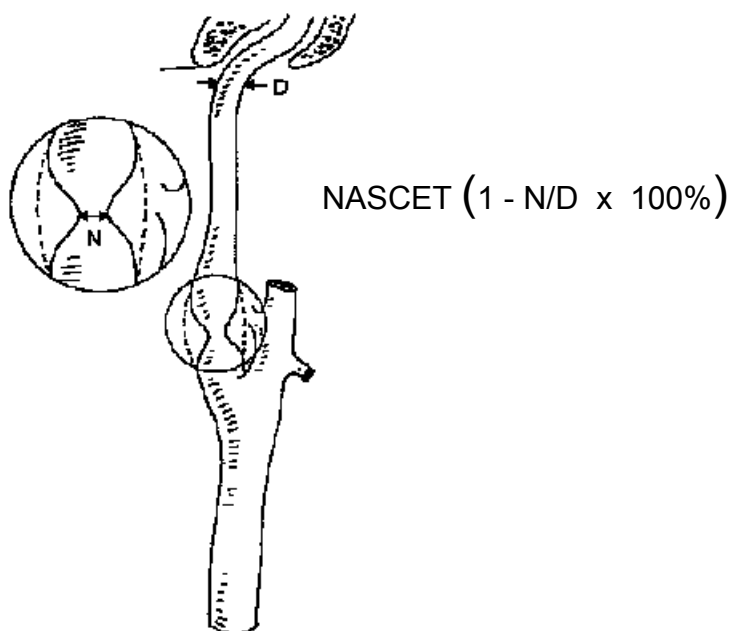
Zweibel W – 1994 (Ultrasound criteria)

Diameter stenosis	PSV cm/s
50%	120-150
60%	150-170
60-70%	170-220
70%	220-250
70-80%	250-290
80%	290-300
90%	>300

ASUM CRITERIA

<u>Stenosis grade</u>	Ultrasound criteria - ICA
0	Normal waveform and image
<15% diameter reduction	Deceleration spectral broadening PSV <125 cm/sec
16-49% diameter reduction	Pansystolic spectral broadening PSV <125 cm/sec
50-69% diameter reduction	Pansystolic spectral broadening PSV >125 cm/sec and EDV <110 cm/sec or ICA/CCA >2
70-79% diameter reduction	Pansystolic spectral broadening PSV >270 cm/sec or EDV >110 cm/sec or ICA/CCA >4
80-99% diameter reduction	As above plus EDV > 140 cm/sec
Occluded	No flow Terminal thump

ICA Internal Carotid Artery
 CCA Common Carotid Artery
 PSV Peak Systolic Velocity
 EDV End Diastolic Velocity
 ICA/CCA Ratio of ICA PSV to CCA PSV



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