

ASA and Carotid Endarterectomy (ACE) Trial

Research Protocol

**A Randomized Trial of ASA Dose in Patients
Scheduled for Carotid Endarterectomy**

NASCET Collaborative Study Group

ACE Coordinating Center:

*Department of Clinical Epidemiology & Biostatistics
McMaster University, Chedoke Division Building 74
1200 Main Street West
Hamilton, Ontario, Canada L8N 3Z5*

ASA & CAROTID ENDARTERECTOMY (ACE)

RESEARCH PROTOCOL

1.0 RESEARCH OBJECTIVE

Recent evidence from 2 large clinical trials has firmly established the benefit of carotid endarterectomy (CE) for patients with symptomatic high grade carotid stenosis, and a trial in asymptomatic patients, published in 1993, reported benefits of CE using the combination of transient ischemic attacks (TIA) and stroke as outcome events. Trials currently underway will further define the role of this surgical procedure for asymptomatic patients and for those with more moderate carotid stenosis. The increased scientific investigation of CE, and discovery of a reduction in fatal and non-fatal stroke following the procedure, has led to an increase in the use of CE. This is likely to continue. Although CE produces long term benefits, there is also a substantial immediate perioperative risk of stroke and death. Consequently, it is crucial that we investigate means of reducing this risk.

An uncontrolled observation from the NASCET trial suggests that it may be possible to reduce the perioperative risk of CE through a simple regimen consisting of a daily dose of 650 to 1300 mg of ASA started prior to surgery. Although the value of ASA in stroke prevention has been clearly established over the last decade, disagreement exists over the appropriate dose for primary prevention and no useful information exists on dosage effects in patients undergoing surgery to the carotid artery. In the proposed trial, patients scheduled for carotid endarterectomy at centers currently participating in the NASCET collaborative study group, will be randomly assigned, before surgery, to one of 4 drug regimens consisting of ASA at a daily dose of 81 mg, 325 mg, 650 mg, or 1300 mg, to be continued for 90 days. These patients will be followed for 3 months from surgery to record all strokes, deaths and changes in functional status. These outcomes will form the basis for the comparison of the 4 ASA dosage groups.

Approximately 100,000 individuals undergo CE in the U.S.A. and Canada each year. Currently about 6%, or 6000, of these patients suffer stroke or death within 30 days of surgery. A 50% reduction in this event rate would thus spare 3000 individuals from stroke and death each year, and would give increased confidence to both those offering and those receiving this surgical procedure. The proposed trial will determine whether such benefits exist and provide the information needed to estimate the magnitude of risk reduction that might be achievable with a simple ASA treatment regimen.

1.1 PRIMARY RESEARCH QUESTION

Among patients who undergo carotid endarterectomy, is the risk of stroke and death in the 30 day perioperative period, and in the first 3 months after surgery, influenced by the prescription of high doses of ASA (≥ 650 mg/day) vs. low doses of ASA (≤ 325 mg/day), started prior to surgery, and continued for 3 months?

1.2 SECONDARY RESEARCH QUESTIONS

- 1) Is there any difference between the 2 lower doses of ASA (81 mg vs. 325 mg) in the perioperative risk of stroke and death?
- 2) Is there any difference between the 2 higher doses of ASA (650 mg vs. 1300 mg) in the perioperative risk of stroke and death?

2.0 BACKGROUND

Carotid Endarterectomy (CE) has been practiced since the mid 1950s for the prevention of stroke in patients with carotid stenosis. Although 2 randomized controlled clinical trials,^{1,2} one published in 1970 and the other in 1984, failed to demonstrate a benefit of CE in symptomatic patients, neither trial was considered definitive. During this period the frequency of CE increased dramatically, rising in non-Veterans Hospitals in the USA from 15,000 in 1971 to 82,000 in 1982, and 107,000 in 1985.³

The first clear evidence of benefit from CE came in 1991 with the publication of the North American⁴ and European⁵ trials of CE in symptomatic patients with severe carotid stenosis (70-99% based, in NASCET, on a linear comparison of the narrowest section of artery at the stenosis with the normal artery beyond the bulb). The benefit was so dramatic that the NASCET trial crossed its stringent ($p < .001$) stopping rule, with a total of only 659 patients and an average follow-up of only 18 months. Surgery had reduced the risk of a fatal or non-fatal ipsilateral stroke over the ensuing 2 years to 9%, compared to 26% among those patients randomized to medical care without surgery, and the risk for all stroke and death dropped from 32% to 16% (Appendix A, Table 2, page 448). Results reported from the European trial were similar. Both the NASCET and European trialists reported that their stopping rules were not triggered for patients with less severe carotid stenosis, and hence both trials are continuing to randomize and follow symptomatic patients with moderate stenosis (30-69%).

The value of CE for asymptomatic patients with carotid stenosis is less clear. Although 2 previous trials failed to show a benefit of CE,^{6,7} a recently published trial⁸ reported that CE prevented the development of cerebrovascular events (defined as TIA or stroke) in these patients. This has been interpreted by some as justification for operating on asymptomatic patients with carotid stenosis. However, because no benefit was observed for stroke alone, others have caution against over interpretation of these results.^{9,10} We can look forward to further clarification of this issue when the ACAS trial,¹¹ currently in progress, is completed.

While the ongoing trials will continue to define the characteristics of those patients who can be expected to benefit from CE, this surgical procedure has been clearly established as beneficial in severe symptomatic disease, and some are now convinced that it is also beneficial for asymptomatic patients. Consequently, the use of this procedure is rapidly rising and will probably continue to increase until the correct target population for this procedure is more clearly defined.

Although CE produces long term benefits it also has significant immediate risks. A retrospective national survey of US centers¹² found a perioperative stroke and death rate of 6.2%, and from the

4 recently published trials^{4,5,6,8} we have current estimates which range from 5.8% to 7.6%. Given this level of risk and the growing interest in CE, it is clearly important to attempt to identify means of reducing the immediate perioperative morbidity and mortality associated with this surgical procedure.

Reports of Perioperative Risk (30 day)
From Recent Studies of Carotid Endarterectomy

| | |
|------------------------------|------|
| USA National Survey | |
| Fode et al, 1986 | 6.2% |
| Symptomatic Patients | |
| NASCET Trial, 1991 | 5.8% |
| European Trial, 1992 | 7.6% |
| Asymptomatic Patients | |
| CASANOVA Trial, 1991 | 6.9% |
| VA Trial, Hobson et el, 1993 | 5.9% |

2.1 NASCET OBSERVATIONS

An analysis of perioperative stroke and death by dose of ASA at randomization, among NASCET⁴ surgical patients with severe carotid stenosis, revealed a difference in favor of higher doses of ASA. The 30 day perioperative risk of stroke or death for patients taking none, 325mg/day, 650mg/day and 1300mg/day was 7.8%, 6.5%, 1.1% and 2.7% respectively. No difference in baseline characteristics that might explain these results was observed.

Perioperative Risk (30 day) of Stroke and Death
By ASA Dose At Randomization in NASCET

| ASA Dose | Stroke / Death | Patients | Risk |
|---------------|----------------|----------|------|
| none | 4 | 51 | 7.8 |
| 325 mg / day | 7 | 108 | 6.5% |
| 650 mg / day | 1 | 94 | 1.1% |
| 1300 mg / day | 2 | 74 | 2.7% |

Comparing the 159 patients on 0-325mg/day vs. the 168 patients on 650-1300 mg/day, gives perioperative event rates of 6.9% and 1.8% respectively, for an absolute difference of 5.1% in favor of the higher doses of ASA. Although these results reach statistical significance ($p=.028$, 2 tailed Fisher's exact test) they are not conclusive because patients were not randomized to these doses of ASA, the combination of the 2 lower and 2 higher doses was not specified before hand and may be fortuitous, patients did not necessarily remain on the dose of ASA they presented with prior to surgery, and patient compliance was not assessed with the diligence that would be required of a trial of drug dosage levels. Nevertheless, the observed absolute difference of about 5% is extremely important if real.

Given the large number of carotid endarterectomies performed each year, (using the best available data we estimate about 100,000 operations per year in North America alone)³³, a 5% absolute difference translates into the possibility of preventing 5000 strokes per year. Even if the current observation is overly optimistic the prevention of even half this number of strokes would be important given the low cost, risks and ease of administration of a short course of ASA.

2.2 BIOLOGICAL RATIONALE

If the striking, but non-randomized, observation from the NASCET trial resulted from a dose-dependent alteration in platelet function, it requires an explanation beyond the dose-independent inhibition of Thromboxane A₂.¹³ One potential candidate is the dose-dependent lipoxygenase pathway leading to 12 HETE and enhanced platelet adherence, as measured for example in shortened simple platelet bleeding times. This pathway is stimulated, not inhibited, by low dose aspirin.¹⁴ Other evidence suggests a direct relationship between the strength of the thrombotic stimulus and the ASA concentration required to prevent clot formation.¹⁵ The extensively denuded carotid artery wall following endarterectomy may present a strong thrombotic stimulus and may thus be especially vulnerable to platelet adherence.

Neither alternative (low dose ASA inhibition of Thromboxane A₂, nor high dose ASA inhibition through the lipoxygenase pathway) has gained widespread acceptance, due perhaps to the wide variety of experimental models and different aspects of platelet activity measured in different laboratories. For example, low dose ASA has been shown to be as effective as high dose ASA when measuring thromboxane A₂ levels or aggregation in the presence of high dose ADP in platelet rich plasma.¹⁶ On the other hand, there is a clear dose-dependent effect of ASA (with higher doses being more effective) in decreasing in vitro shear-induced platelet thrombus formation,¹⁷ as well as in inhibiting platelet aggregation in the presence of either low dose ADP or collagen.¹⁶ To further demonstrate that different measurements can lead to different interpretations, it has been shown, within the same study, that increasing doses of ASA both increase tail transection bleeding time and decrease template bleeding time.¹⁸

Finally, the observation that ticlopidine, a drug which does not act through the arachidonic pathway to alter levels of either Thromboxane A₂ or of prostacyclin, still alters platelet function in a sufficiently meaningful way as to prevent stroke, indicates that other less clearly understood pathways have clinical importance.

2.3 PREVIOUS ANIMAL & CLINICAL TRIALS

Because of the lack of consensus at the biochemical level, the major rationale for this trial comes from studies in intact animals and patients. It has been shown that administration of ASA prior to carotid endarterectomy has a favorable effect on platelet aggregation¹⁹ and patency rates²⁰ in animal models. A favorable effect of ASA has also been shown on neurological complications^{21,22} and long-term (but not perioperative) survival²³ in humans.

Kretschmer et al²³ randomized 66 patients to ASA (1000 mg/day) or placebo started 2 days before surgery. Over a 4 year follow-up there were 4 deaths on ASA and 11 on placebo (p<.048). The design of this trial was appropriate to the question of perioperative risk reduction with high

dose ASA but it was far too small. None of the reported deaths occurred within the first 3 months after surgery and no information was reported on stroke.

When started 1-12 weeks after carotid endarterectomy, no reduction was seen in cerebrovascular complications, for low dose ASA (50-100 mg/day) compared to placebo.²⁴ However, with only 150 patients per treatment group this trial was much too small to focus on perioperative events, and treatment with ASA may have been started too late.

The optimal dose of ASA is unclear even for secondary prophylaxis in non-surgical patients.²⁵ The early trials,^{26,27} using 1 gm or more per day, demonstrated marked reductions in both fatal and non-fatal cerebrovascular events, and a recent secondary prevention trial²⁸ found a benefit for very low dose ASA (75 mg/day) compared to placebo. However, the degree of benefit found in the low dose studies²⁹, has been substantially less than that seen in the older high dose studies. Also, in the US Physicians Health Study³⁰ which included 22,000 men, low dose ASA (325 mg every other day) was found to reduce the risk of myocardial infarction by 46%, but had absolutely no effect on the risk of stroke (which was slightly higher in the ASA group compared to placebo).

Finally, the relevance of the secondary prevention trials to the research question posed in the present application is unclear, as the mechanisms responsible for thrombus formation at the endarterectomy surgical site may be quite different from the mechanisms operating in intact carotid arteries.

2.4 CLINICAL SIGNIFICANCE

We and our surgical and neurological collaborators across North America consider the proposed trial to be a very high priority for the following reasons:

1. the intriguing relationship observed between ASA dose and perioperative risk from the NASCET trial suggests that a simple and inexpensive treatment might substantially reduce the immediate risk of stroke and death for CE patients
2. continuing uncertainty regarding ASA dose for stroke prevention leaves many clinicians unsure about the optimal dose of ASA
3. a trial of sufficient size has not yet been conducted to address the question of ASA dose in the perioperative period
4. the large number of carotid endarterectomies performed each year expose large numbers of patients to the immediate risk of stroke and death from CE itself
5. the growing interest in this procedure in the wake of recent reports of surgical benefits will translate into further increases in the use of CE
6. the relatively high risk associated with this procedure (approximately 6% suffer stroke or death within 30 days of surgery) limits its usefulness and deters some patients who could benefit from it
7. the inclination of many clinicians to go to high dose ASA on the basis of the uncontrolled NASCET observations might actually have an as yet undetermined detrimental effect on patients who require CE

3.0 RESEARCH DESIGN

The primary research question (see 1.1) will be addressed using a blinded, randomized controlled trial, involving 2800 patients from 75 NASCET centers in the USA and Canada. Prior to surgery, patients will be randomized, within center, to one of 4 treatment groups, which will differ only in the dose of ASA prescribed (81, 325, 650 or 1300 mg/day). Treatment will continue for 3 months. Patient assessments will occur at baseline, surgery, hospital discharge, 30 days, and 3 months.

3.1 PARTICIPATING CENTERS

This trial will be conducted in those clinical centers currently participating in the North American Carotid Endarterectomy Trial (NASCET). Each center has a least one participating surgeon, neurologist, and neuroradiologist, plus a research coordinator responsible for recruiting patients, scheduling follow-ups, and submitting case report forms. Both neurosurgeons and vascular surgeons will be involved in the trial. Each center was approved for the NASCET trial based on a review of their most recent 50 cases, which had to show a perioperative risk of stroke and death of less than 6%.

3.2 PATIENTS

Patients are eligible for the ACE trial if they:

- (1) are scheduled for carotid endarterectomy at a NASCET center
- (2) can tolerate the possible maximum dose of 1300 mg of ASA daily for 3 months
- (3) are not already participating in NASCET, or another clinical trial

The perioperative risk for patients participating in the symptomatic^{4,5} and asymptomatic^{6,8} trials published recently are very comparable. Nor have we observed any association between degree of carotid stenosis and perioperative risk in the NASCET trial. Consequently, both symptomatic and asymptomatic patients are eligible, as are patients with severe or moderate carotid stenosis.

Patients will be excluded if they:

- (1) are unable or unwilling to provide informed consent
- (2) have suffered a recent major stroke in the carotid distribution scheduled for surgery
- (3) are taking ASA or ASA containing medication which can not be stopped for the 3 month treatment period
- (4) are taking some other anti-platelet medication which can not be stopped for the 3 month treatment period
- (5) are already taking 325 mg or more of ASA per day and are scheduled for surgery in less than 48 hours since their last dose of ASA

Patients who have already suffered a devastating stroke in the distribution of the carotid stenosis considered for carotid endarterectomy will not be eligible for the trial, as it would be difficult to identify a new perioperative event in such cases. Patients who have suffered a recent devastating stroke would rarely be considered appropriate surgical candidates in any case.

Some patients (e.g. those who present with TIAs or a minor stroke), will have been prescribed ASA before randomization. Although the current trend is toward use of low dose ASA, some of these patients may have been placed on high dose ASA. While these patients will switch immediately to their randomized regimen, we wish to minimize the effect of any prior ASA treatment. There is no reason for concern with patients who are switched from low dose ASA to high dose ASA, but the possibility of contamination of the low dose group exists arising from patients randomized to low dose ASA, who were previously taking high doses of ASA (more than 325 mg/day). To reduce this possibility, patients who are already taking 325 mg or more of ASA per day will be excluded from the trial if they are scheduled for surgery in less than 48 hours following their last dose of ASA. This will provide at least 2 days to lower the effect of the previous dose of ASA in patients randomized to low dose ASA.

3.3 SURGERY

Surgeons will not be restricted in any way with regard to operative procedures. Surgical technique and concurrent medications including: use or non-use of patch closure, type of vein patch employed, dose of heparin anticoagulation during application of cross-clamps, and reversal or nonreversal of protamine sulfate, will all be at the discretion of the surgeon. These and other details of surgery will be recorded and used as covariates during the statistical analysis.

3.4 ASA TREATMENT GROUPS

Patients will be randomly assigned, prior to surgery, to one of 4 ASA treatment groups: 80, 325, 650 or 1300 mg of ASA per day. A fifth placebo group was considered but rejected. Although the optimal dosage of ASA that should be prescribed for stroke prevention may be in question, the benefit of ASA in reducing the risk of stroke, in patients who have experienced cerebrovascular symptoms, is not. Many of the patients who will participate in the ACE trial will have recently experienced TIAs or small strokes and thus it would be unethical to withhold from them a treatment known to be effective. Also, the absence of a placebo, and the realization that all patients will receive active treatment, makes it easier for many patients to agree to participate, which should thus make patient recruitment goals easier to achieve.

Treatment will begin immediately on the day of randomization and continue until the final 3 month assessment. Participating physicians are then free to change the ASA regimen to whatever dose they consider appropriate for long term maintenance, or to switch to another anti-platelet regimen.

ASA will be delivered to patients in blister packs, each containing sufficient medication for 1 week. The medication for each day will consist of 5 pills. All pills will be enteric coated. Patients will be instructed to take 3 pills in the morning with breakfast and 2 pills in the evening with dinner. They will further be instructed to take the morning and evening doses together if they forgot to take the morning dose, but to never take more than 1 days worth of pills on any given day.

The first pill for each day is a little smaller than the others. It will contain 81 mg of ASA for the 81 mg treatment group, and placebo for all other groups. All of the other pills will contain either 325 mg of ASA or placebo, as appropriate to construct the 4 study dosage levels (80, 325, 650 and 1300 mg/day).

3.5 PATIENT RANDOMIZATION & DRUG DISPENSING

A patient randomization schedule will be generated by computer for each of the participating centers. Randomization will balance periodically on the number of patients receiving each dose of ASA within each center. Two block sizes will be used, and varied randomly within each center's randomization schedule.

Each participating center will be provided with a 6 month supply of patient randomization packages, based on their prior estimate of the number of cases they expect to be able to recruit per year. Each package will consist of an opaque, sealed folder, pre-labeled with a patient study number and containing a complete set of patient case report forms and blister pacs of study medication. These envelopes will be kept in a safe place by the research coordinator at each center. Use of the randomization packages will be monitored centrally, through receipt of the one page randomization form which is to be faxed, for each patient, on the day of randomization. Centers will be contacted and additional packages shipped as required to ensure no interruptions in patient recruitment.

Patients will be recruited for the trial as soon as possible once carotid endarterectomy is scheduled. Randomization packages will be used in sequence by patient study number, which will be printed on the outside of each envelope.

After checking that the patient meets the study criteria (which will also be printed as a reminder on the outside of each envelope), and the patient has agreed to the trial and signed a study consent form, the patient's name and the date of randomization will be printed on the outside of the envelope and it will then be opened. This act constitutes entry and randomization of the patient into the trial.

Each randomization package will contain a one page patient entry form which will be completed and faxed immediately to the data management office to register the patient into the trial. It will be the research coordinators responsibility to see that the remaining case report forms (baseline, surgical report, hospital discharge, 30 day follow-up, and 3 month follow-up) are completed and faxed as soon as possible after each assessment has been performed.

As soon as the package is opened the patient will be given a medication blister pac and asked to take all 5 pills for the first day. The patient will also be asked to bring their study medication with them to the hospital on the day of surgery so that study medication can continue while the patient remains in hospital. The remaining blister pacs will be dispensed as required to ensure than the patient has sufficient medication to last until the next study assessment, as judged appropriate by the local study coordinator.

Although this trial will not use a central randomization system it is to a certain extent protected from intentional tampering by the use of enteric coated and blister packed medication. Further, since all of the doses of ASA under study are used in clinical practice, and the physicians participating in this trial do not hold strong views on which dose of ASA to recommend, we have very little concern regarding the possibility of intentional tampering with randomization packages. The ease of randomization which this approach provides is likely to be more important (for patient recruitment) than the protection against intentional fraud which could be provided by

a more complicated system.

3.6 AVOIDANCE OF CONTAMINATION AND COINTERVENTION

Only patients who are able to discontinue medications containing ASA, and other anti-platelet medications will be included in the trial. Patients will be instructed to avoid aspirin and other medications containing ASA during the 3 months of the trial. Further, they will be instructed in other medications which may be used, if necessary, for pain relief (e.g. Tylenol).

3.7 SAMPLE SIZE

Our best estimate of the risk of stroke and death that will be observed in the ACE trial in the 30 day perioperative period following carotid endarterectomy is 5.8% (from the NASCET trial). However, both the NASCET trial and the European trial (where a greater bias toward low dose ASA exists), suggest that the perioperative risk with low dose ASA may be as high as 7% or 8%. The following table shows sample size requirements per treatment group, for a 2 group comparison, using a 2 tailed type 1 error rate of .05, and a power of .90.

| Sample Size Per Treatment Group For a 2 Group Comparison at $\alpha = .05$, 2 tailed; $\beta = .1$ | | | | | |
|--|-------------------------|-------|-------|-----|-----|
| Perioperative Risk | Absolute Risk Reduction | | | | |
| | 1% | 2% | 3% | 4% | 5% |
| 8 % | 14,550 | 3,400 | 1,400 | 720 | 420 |
| 7 % | 12,750 | 2,940 | 1,190 | 600 | 340 |
| 6 % | 10,890 | 2,470 | 980 | 480 | 250 |
| 5 % | 9,000 | 1,990 | 760 | 340 | |
| 4 % | 7,060 | 1,490 | 520 | | |

The table shows sample size requirements for absolute risk reductions of 1% to 5%, against perioperative risks of 4% to 8%. Absolute reductions are shown because of their ease of interpretation. Regardless of the baseline risk, an absolute risk reduction of 1,2,3,4 or 5%, means that we can prevent perioperative stroke and death in 1,2,3,4 or 5 patients per hundred operations.

From the above table it is clear that sample size requirements vary dramatically depending on assumed perioperative risk and absolute risk reduction; and thus will produce correspondingly dramatic differences in our determination of trial cost and feasibility. The use of a 2 tailed test at the .05 level, and a power of 90% is standard for large cooperative trials addressing important clinical questions. Given we accept the type 1 and type 2 error rates as fixed at these levels, the selection of sample size then represents a balance among 3 considerations:

1. the size of treatment effect we would consider clinically important to detect (if real),
2. the size of effect prior evidence suggests we might expect to observe,
3. and the cost and feasibility of successfully assembling the required patients.

The NASCET observations described previously showed a reduction in perioperative risk from 6.9% (11/159) for low dose ASA (≤ 350 mg/day) to 1.8% (3/168) for high dose ASA (≥ 650 mg/day); an absolute risk reduction of 5.1%. Thus some evidence exists that a large effect may be possible. However, it is prudent to adopt a more conservative estimate of the true degree of risk reduction. Estimates which arise from uncontrolled observations, and which are strong enough to suggest the need for a clinical trial, are often an exaggeration of true treatment differences. Using them could lead to a trial with too few patients to detect a smaller but important treatment effect.

What is the smallest degree of risk reduction that would be considered clinically important to detect if it exists? Although answers to this question will vary, the low cost and ease of administration of ASA, and the seriousness of the events we are trying to prevent, argue for an answer well below 5%. Even a 1% or 2% difference could be defended. If we estimate that 100,000 carotid endarterectomies will be performed in the U.S.A. and Canada each year, then a 1% risk reduction translates into the prevention of 1,000 strokes and deaths per year. However, it is clear that mounting a trial large enough to guarantee that a 1% difference could be detected would be both difficult and expensive. Further, the NASCET observation of a 5% risk reduction suggests that such a large trial may not be necessary.

The feasibility of assembling the required number of patients is addressed by the estimates provided by the NASCET centers (Appendix F). These estimates, based on those centers which have responded to date, indicate that we can expect to enroll about 1900 patients per year. Thus in a 3 year trial we might hope to be able to assemble 5700 patients. Recognizing that such prior estimates are often optimistic, but that the NASCET team is experienced and successful, we are confident that we can assemble at least half this number (2850).

In balancing these considerations we have decided to plan the trial large enough to have 90% power for the primary question if the true absolute risk reduction is 3% or more against perioperative risks in the range 4% to 8%. This leads to a total sample size of 2800 patients, 700 in each of the 4 treatment groups. For the primary question the 2 lower dose groups will be combined and compared to the 2 higher dose groups combined. Thus for this analysis there will be 1400 patients per treatment group.

For the 2 secondary questions we will have 700 patients per group. The above table shows that this will provide 90% power if the risk reduction is high (4% or more) across all estimates of perioperative risk, and is also adequate to detect a 3% risk reduction if perioperative risk is below 5%.

An interim analysis, described under "3.14 Statistical Analysis" below, may bring the trial to an early conclusion at a lower sample size.

3.8 PROJECTED STUDY DURATION

Given the large number of patients that will be eligible for the trial, the simplicity of the protocol, the expected relative ease of obtaining patient consent (compared to NASCET), and the wider eligibility criteria (compared to NASCET which only includes symptomatic patients with moderate stenosis and excludes patients with certain medical conditions), we expect a more rapid

recruitment than NASCET, which is currently enrolling approximately 30 patients per month. We estimate enrollment for the ACE trial at 100 patients per month. This will assemble 2800 patients in 28 months, and represents less than 2 patients per month from each of the 75 participating NASCET centers.

Since each patient will be followed for only 3 months the total duration of the trial is estimated at $28 + 3 = 31$ months. Funding is requested for 3 years to allow an extra 5 months for trial start up, additional time for patient recruitment if required, and time to finalize the database and perform the statistical analyses.

We believe that this is feasible for the following reasons.

3.9 FEASIBILITY

The trial proposed in this application (ACE) will be conducted by the same clinical centers that are currently participating in the North American Symptomatic Carotid Endarterectomy trial (NASCET).

This is **a research team with a proven track record**. They have:

1. demonstrated that they can successfully recruit patients for a much more difficult trial.
2. successfully completed the first phase of NASCET, which saw publication of the first definitive results to show a benefit of carotid endarterectomy (CE) in patients with high grade stenosis.
3. are continuing to randomize patients with high grade stenosis to determine the value of CE in symptomatic patients with milder degrees of stenosis.
4. expanded from the initial 50 centers to the current 83 in order to ensure that sample size targets would be reached.
5. shown their dedication to clinical research and to obtaining solid answers to the research questions posed, by their continuing participation and support over the past 6 years, despite severe budget limitations which have resulted in no increase in center payments over this period, and reductions in central office, data management and statistical support budgets.
6. the ACE trial will have the benefit of the NASCET team, and particularly the research coordinators, who are already trained and familiar with both clinical trial procedures, and with clinical practice procedures and individuals in their centers.

The ACE trial employs a **simple design and execution strategy** which is expected to make this trial particularly easy to implement. It is a considerably simpler trial than NASCET for the following reasons:

1. The ACE trial will have very few patient entry restrictions compared to NASCET. NASCET enrollment is limited to symptomatic patients with moderate stenosis, i.e. < 70%, who meet strict medical eligibility criteria. The target patient population for the ACE trial includes asymptomatic patients and involves no restriction on degree of carotid stenosis. Nor does ACE exclude patients who have medical conditions which limit their

- probability of survival over the next 5 years.
2. Obtaining patient consent should be much easier than for the NASCET trial. All ACE patients will receive active study treatment (ASA at different dose levels), using a drug which is well known and commonly used in the dose levels under study.
 3. Patient case report forms have been reduced to essential data only and centers are not required to submit angiographic films and doppler recordings for central review.
 4. Patient entry and randomization can be performed by the center, from sealed study randomization packages. Thus, although it requires faxing a 1 page randomization form to the study coordinating center within 24 hrs, it does not require any need to contact the study management office in any way to obtain the random assignment.
 5. Study follow-up is very short, ending for each patient at 3 months. NASCET patients by comparison are followed every 4 months for the entire duration of the trial (maximum of 10 years for the first patient randomized).

Most NASCET centers have agreed to join the ACE trial. The discovery of improved survival from stroke and death with CE, in symptomatic patients with high grade stenosis, has led to considerable interest in the investigation of approaches to patient management which might reduce the immediate perioperative surgical risks. The investigation of different dosage levels of ASA is particularly attractive because the issue of ASA dose remains controversial among clinicians treating patients threatened with stroke, and because ASA is well known, simple and inexpensive to deliver.

The NASCET team responded very positively to the proposed ACE protocol when presented with a preliminary design at the last annual investigators workshop, and have demonstrated their commitment by their replies to a request for letters of interest. These centers have estimated a combined annual enrollment of between 1860 and 1930 patients per year (155 to 160 per month). At this rate the required 2800 patients could be assembled in 18 months. Because the NASCET investigators are experienced with patient recruitment we expect that their estimates are considerably more accurate than those provided by most beginning research teams. However, we have conservatively reduced this estimate to 100 patients per month in planning the trial. Even at this rate the ACE trial will assemble the required sample size in 28 months and thus we are confident that the trial can be completed within the proposed 3 year time frame.

Patient accrual will be carefully monitored each month and summarized in a report which will be sent to all participating centers and carefully reviewed by the Principal and Co-Principal Investigators. Centers which fail to meet recruitment targets will be contacted personally by fax and phone to discuss recruitment problems and possible solutions.

3.10 BASELINE ASSESSMENTS

Baseline forms, to be completed upon entry to the trial, will include: a brief medical history, neurological assessment, functional status, current medications and doppler and angiographic imaging results. Films (doppler and angiography) will not be submitted to the NASCET coordinating center for central review (as is performed in the NASCET trial). This is not considered necessary because assessment of the degree of stenosis is not central to this trial, as it

is to NASCET, and because the participating clinical sites are now familiar with the NASCET criteria for measuring carotid stenosis. We will thus only collect the measurements provided by the participating centers and avoid the cost and effort that would be involved in the central review of imaging films and recordings.

3.11 SURGICAL ASSESSMENTS

A 2 page surgical report based on the one which is currently used in the NASCET trial will be completed to describe the operation, including: anesthetic used, blood pressure and blood gases, type of cerebral monitoring employed, use of anticoagulants, etc.

3.12 FOLLOW-UP ASSESSMENTS

Follow-up assessments will occur at discharge from hospital, and at 30 days and 3 months following surgery. The hospital discharge report will include both minor and major post-operative complications (including stroke and death), and a functional status assessment. The 30 day and 3 month assessments will include current functional status, intercurrent cerebrovascular events (TIA and stroke), changes in medical or neurological status, and intercurrent medication history (with particular attention to the use of ASA and compounds containing ASA). The blister packs of study medication will be collected at the 30 day and 3 month follow-up assessments and the number of pills remaining will be counted and recorded to assess patient compliance.

3.13 PATIENT FUNCTIONAL STATUS ASSESSMENTS

Patient's functional status will be assessed at randomization, at hospital discharge, and at the 1 month and 3 month follow-up visits, using the NASCET functional status instrument. Patients will be rated by the study neurologist at each center on each of 11 7-point scales (1=normal function, 7=no function) including: vision for reading, vision for ambulation, comprehension, fluency, getting in and out of bed, sitting down and standing up, walking, personal hygiene, dressing and undressing, cutting food and pouring beverages, swallowing, ability to shop and ability to visit friends and family. These categories were originally derived from a validated index of Activities of Daily Living by Katz et al, and further refined and validated in the Extracranial-Intracranial Bypass (EC/IC) trial.

Analysis of functional status among NASCET patients with high grade stenosis shows a statistically significant difference in favor of surgical patients during follow-up, which mirrored the significant benefit found for surgery in stroke prevention, thus providing further validation for this scale.

3.14 STROKE AND DEATH ADJUDICATION

All stroke and death reports will be reviewed by a blinded adjudication committee as soon as possible after each stroke and death report is received. This committee will be comprised of neurologists and surgeons at the NASCET clinical coordinating center (Robarts Research Institute, London, Ontario, Canada) who will review all documentation on each event, request additional information from the clinical sites if necessary, and complete a stroke or death adjudication form (Appendix E) which will identify type, vascular distribution and severity of

strokes and cause of death. Blinding should not be a problem except for the suspicions which may be raised by possible gastric side effects to ASA. The research fellows who present cases for review will thus take special care not to make unnecessary mention of gastric complaints. All decisions made by this committee will be final. Their judgements will form the basis for all subsequent statistical analyses.

3.15 STATISTICAL ANALYSIS

The data management and biostatistical group will be provided with a file containing a coded randomization schedule, but they will not be informed of the ASA dosage level corresponding to these codes. The only persons who will have access to the code during the trial will be Dr. R.B. Haynes, who will supervise the preparation of the randomization packages and chair the study safety and efficacy monitoring committee (SEMC). This will allow the trial management group (including the PI and his staff) to prepare status reports and perform the interim analysis for the SEMC blind with respect to which treatment groups are high and low dose.

The primary research question will be addressed by the comparison of 2 proportions using a chi-square test. Specifically, the 2 high dose groups (650 and 1300 mg/day) will be combined and compared with the combined low dose groups (80 and 325 mg/day), on the proportion of patients suffering stroke (of any type) or death (from any cause) in the 30 day perioperative period.

The 2 secondary research questions will be addressed by the same tests for the 2 orthogonal contrasts: 80 vs. 325 mg/day, and 650 vs. 1300 mg/day.

Similar analyses will be performed using all strokes and deaths occurring between randomization and the final 3 month follow-up.

All of these analyses will follow the intention to treat principle, specifically:

1. All patients entered into the trial and randomized will be included in the analysis, regardless of compliance with treatment, or any other deviation from protocol.
2. Because the entry criteria are simple and do not rely on sophisticated tests and investigations we do not anticipate problems caused by the entry of ineligible patients. However, any patient discovered to have been ineligible at entry will be included in the final analysis, to avoid any suspicion of tampering with the results.
3. We do not expect to have any patients lost to follow-up. No patients were lost in the first phase of the NASCET trial which has been published. The ACE trial involves a much shorter (3 month) follow-up, at a time when patients are recovering from surgery and expected to keep follow-up appointments. However, if a patient refuses to return for a follow-up assessment his/her status with regard to stroke/death and changes in functional status will be determined by phone contact with the patient and/or the patients family physician.
4. Any strokes or deaths which occur after randomization but prior to surgery will be included in the intention to treat analysis.
5. Any strokes or deaths which occur after randomization and which might be attributed to

pre- or post-operative investigations will be included.

6. All types of stroke and all causes of death will be included.

Additional analyses, employing logistic regression, will examine, and control for, the influence of patient and surgical factors which might be associated with the risk of perioperative stroke and death including: degree of stenosis, presence/absence of ulceration, medical conditions (e.g. diabetes, prior myocardial infarction, hypertension, etc.), recency and type of cerebrovascular events, ASA regimen prior to randomization, use of heparin during clamping, type of cerebral monitoring, type of arteriotomy closure, and appearance of the plaque during surgery.

In addition to stroke and death, the treatment groups will also be compared on the occurrence of other surgical complications (eg. wound problems and nerve damage) and events which may be attributable to ASA (eg. increased need for transfusions, the formation of haematomas, GI bleeding and gastric pain). These analyses will also be performed using Pearson's chi-square test, and logistic regression.

Finally, treatment groups will be compared on change in mean functional status scores at hospital discharge, and at the 30 day and 3 month follow-up exams, using analysis of variance.

3.16 INTERIM ANALYSIS AND STOPPING RULES

Interim analyses will be performed when half of the planned sample size, i.e. 1400 patients, 350/ treatment group, have completed the trial. The results of these analyses, including confidence intervals, will be presented to an independent efficacy and safety monitoring committee (chaired by Dr. R.B. Haynes). This committee will be charged with considering all of the available data, and will then advise the study Executive on whether the trial should be continued or stopped. They will be guided by a pre-specified stopping rule, namely that we would wish to stop early if the primary analysis reaches a p-value of .001. If this level of statistical significance is not reached, and there are no other compelling reasons why the trial should be stopped, we would wish them to recommend that the trial continue to completion.

This strict stopping rule allows the final analysis to be performed at the conventional .05 level of significance, thus maintaining the planned power of 90% for the trial. Given the anticipated low rate of perioperative stroke and death (about 5% overall) and the expected short duration of this trial (3 years) more frequent interim analyses can not be justified.

4.0 DATA MANAGEMENT

Data collection and quality control will be performed using the DataFax system which will be set up and administered for this trial by its originators at McMaster University. A brief description of DataFax procedures follows.

All data will be transmitted by fax from the clinical sites, as soon as possible after each patient assessment. These faxes will be received by the DataFax computer system at McMaster where each page will be automatically scanned, the data entered into the study database, and the faxed data forms saved to computer disc. Research staff will then review each page in a split-screen

window on their computer screens, to review both the faxed data forms and the corresponding database records. They will complete and correct data records as necessary, flag any problems (e.g. missing data) seen on the faxed case report forms with quality control (QC) notes, and fax QC reports containing these data clarification requests back to the research coordinator at the participating NASCET clinics.

In addition to the QC reports, participating centers will also receive a monthly study status report, showing, for each center, the number of: patients entered into the trial, completed follow-ups, outstanding data clarification requests, and overdue assessments. Centers will be identified by number to preserve their anonymity but each center will be able to compare their performance with that of all other centers. The Principle Investigator will keep a close watch on center performance and contact centers by phone, when necessary, to discuss any problems that may arise.

4.1 DATA MANAGEMENT OFFICE PROCEDURES AND RESPONSIBILITIES

The data management office at McMaster will be comprised of 2 full time clinical trial management staff (a Research Coordinator and a Statistician/Programmer), and 3 half time staff (2 data entry clerks and a secretary).

The **Data Clerks** will review all incoming data faxes, complete data entry to validation level 1, enter drug and medical condition codes, and flag any obvious problems (i.e. missing and illegal values) with DataFax quality control (QC) notes. Each data clerk will perform primary data entry (DataFax Validation level 1) on half of the incoming data forms, and will perform secondary review (DataFax Validation level 2) on the primary data entry performed by the other data entry clerk. These individuals will support and work under the direct supervision of the study Research Coordinator.

The study **Research Coordinator** will be responsible for the overall management of the ACE data center, database integrity and quality control, and for all communication with the research assistants at the participating NASCET clinics. This will include:

1. monitoring patient entry and follow-up and maintaining up-to-date status reports for review by the study Principal and Co-Principal Investigators.
2. identifying problem cases (inappropriate patient randomization, overdue follow-ups, missing forms) solving the problems if possible, and if not bringing them forward for discussion at the weekly ACE study management meetings.
3. reviewing all data forms and the corresponding data records (through the DataFax split-screen Validation tool) which have been flagged with quality control notes by the data clerks to identify missing, ambiguous and inconsistent items, to ensure accuracy and consistency in the communication of data clarification requests back to the participating centers.
4. regularly reviewing a random sample of data forms and the corresponding data records (through the DataFax split-screen Validation tool) which have not been flagged with quality control notes by the data clerks to check on the accuracy and completeness of their work.

5. responsibility for creating and transmitting DataFax quality control reports to the participating centers to request data clarifications, missing forms and overdue assessments, on a regular (weekly) schedule.
6. all follow-up communication related to database integrity and quality control with the research coordinators at the participating NASCET clinics.
7. entering all data corrections received, in response to QC reports, into the study database.
8. coordinating the central adjudication of all stroke and death reports. This will include, printing the complete set of data forms for such cases and transmitting them along with any other supporting documentation and films to the endpoint adjudication committee at the Robarts Research Institute.
9. preparing quarterly lists of all new patients completing the 3 month follow-up with complete documentation at each center, to determine the amount of the quarterly payment due to each participating center. These lists will be reviewed with the Principal Investigator and Financial Administrator before each quarterly payment is made.
10. assembling all information required by the Safety and Efficacy Monitoring Committee.
11. supervising the activities of the data entry clerks.

The **Statistician/Programmer** will be responsible for all technical support, database administration, programming and statistical analysis, including: DataFax support (configuring DataFax for the study and maintaining it over the course of the trial), database security and backups, programming database integrity checks and the weekly quality control reports, all programming required to assist the study research coordinator, programming and running the monthly study status reports and seeing that they are successfully faxed to the participating clinics, preparing statistical reports for the study steering, executive and monitoring committees, and performing all interim, final and exploratory statistical analyses.

The **Study Secretary** will provide typing, clerical, communication and organizational support to the Principal Investigator, the Study Research Coordinator and other members of the ACE research group at McMaster University. This will include: typing memos, minutes, reports and manuscripts, correspondence with participating centers, the Co-Principal Investigators, Executive and Steering committee members, NIH officers and committees, and others as required for the conduct of the study, faxing the monthly study status reports and other communications to the participating centers, arranging telephone communications between the Principal Investigator and the participating centers, Co-Principal Investigators and others, organizing ACE Steering committee and other meetings and preparing minutes, telephone answering, xeroxing, filing and other general office duties.

4.2 PATIENT CASE REPORT FORMS

Data collection forms will be kept to the essentials except in the event of stroke and death when more detailed data will be collected. Patient case report forms will include:

1. patient entry form - 1 page, to be faxed the day of randomization
2. baseline forms - risk factors, prior events, imaging data, functional status

3. surgical report - details of surgery
4. hospital discharge report - surgical and other complications, functional status
5. 30 day follow-up - endpoints, functional status and other medical conditions
6. 3 month follow-up - endpoints, functional status and other medical conditions
7. death report form - cause of death
8. stroke report form - type of stroke, including neurological assessment
9. compliance report form - pill counts from returned blister packs

In addition participants will be asked to submit a copy of all baseline and subsequent CAT scans for any patient who suffers a stroke, to aid in stroke adjudication.

5.0 STUDY ORGANIZATION & ADMINISTRATION

In order to minimize costs this trial will rely on much of the organizational structure already in place for the NASCET study. This is possible because the 2 trials will be performed with the same participants and the time frame for completion of the 2 trials coincide.

The NASCET executive and surgical committees will also serve as the executive and surgical committees for ACE. The executive committee meets annually, or more often if required. The surgical committee is responsible for reviewing the surgical performance of a center prior to accepting it into the trial, and for reviewing surgical performance during the trial, to ensure that high surgical standards are maintained.

A weekly meeting will be held at McMaster including the Principal Investigator and all data management staff to review patient accrual, the completeness, quality and timeliness of data collection from each center, and any problems with patients or centers. At least once per month a joint meeting of the NASCET and ACE steering committees will be held to review the status of the 2 trials, present progress reports, review problem cases and endpoint documentation, and discuss any problems with patient recruitment and follow-up.

The safety and efficacy monitoring committee, which will be responsible for reviewing the interim analysis and, if necessary, implementing the studies stopping rule, will be chaired by Dr. R.B. Haynes (Co-PI, Clinical Epidemiology) and will include at least one independent biostatistician and one independent clinician.

6.0 HUMAN SUBJECTS

- (1) The subjects will be of an average age of 64-65, will be 60-65% male and will be no more than 10% black, Hispanic or Oriental. No patients will be excluded because of age, sex or ethnic origin. The disease in the location which we are studying has a predilection for Caucasians. The reasons behind this have failed to be identifiable by population studies. We do not know why it is that there is a racial predilection of arteriosclerosis to affect the extracranial carotid artery of white people and why it is that most other races have a predilection to intracranial carotid disease. All women who have extracranial carotid

artery disease are being invited to enter the trial, as are all people of both sexes in the racial minorities. Biological differences will yield a disparity in the enrollment of women to men, in numerical favor of the latter. It is known that stroke and its threatening symptoms occur later in life in women than they do in men. This may be the only explanation for our tendency to enter slightly more males than females into the NASCET trial. Our centers do not discriminate between the sexes.

The results will be equally applicable to all ages for both sexes and all races. We will have representation in proportion to the occurrence of the disease under study in the whole population.

- (2) The research material consists of health records obtained prospectively from initial and follow up examinations in 3 months. The surgical material from the operations will be dealt with by the pathology departments in the hospitals wherein the patients seek treatment in the standard way that such material is handled.
- (3) Subjects will be recruited in the clinics of the participating institutions. A letter describing the trial and an informed consent form has been crafted for each center, approved by their individual Institutional Review Boards and submitted to and approved by the Office for Protection from Research Risks (OPRR).
- (4) There is a 6% (or less) chance of 30-day perioperative stroke or death related to carotid endarterectomy. The purpose of the ACE trial is to determine if this can be reduced by a short course of treatment with ASA started prior to surgery.
- (5) The surgeons in the trial have been required to submit evidence of their competence, based on their experience with the surgical procedure being studied. The records of the patients are kept in a coded fashion so that their identity is unknown save to their attending practitioner. The confidentiality of the medical records is assured.
- (6) The surgical risks to the subjects are known from the first phase of the NASCET trial to be lower than anticipated from many of the descriptions in the literature evaluating large populations receiving this procedure. The benefit of the procedure in the first part of the NASCET trial was such that there was a 17% absolute difference in 2-year stroke-free survival between those given best medical care and those given the benefit of carotid endarterectomy.
- (7) Stopping Rules will be applied immediately if there is an indication of clear benefit or any evidence of harm to the subjects. This result will be reported to the Executive Committee and as in the First Phase of the NASCET trial, immediate action will be instituted.

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DRAFT PATIENT CONSENT FORM

Study Name: ASA and Carotid Endarterectomy (ACE)
A Randomized Trial Of 4 Doses of ASA For The Prevention Of Peri-operative Stroke In Carotid Endarterectomy

Investigators: NASCET Collaborative Study Group
consisting of surgeons, neurologists, neuroradiologists, epidemiologists and biostatisticians from 80 academic institutions in the USA and Canada

Granting Agency: National Institute of Neurological Disorders and Stroke (NINDS)

I have been asked to participate in this clinical research study because I am scheduled for surgery, specifically carotid endarterectomy, an operation to prevent stroke. There are however serious risks associated with this operation, namely stroke and death, which occur in about 5 percent of patients receiving this operation in North America.

The purpose of this study is to compare 4 doses of ASA (aspirin) for their ability to reduce the risk of stroke and death from the operation, during the 3 month period immediately following surgery. All patients who participate in this study will receive ASA; no one will receive a placebo. The 4 doses under study are 80mg, 325mg, 650mg and 1300mg. In terms of the standard, regular strength, ASA tablets this is equivalent to 1/4, 1, 2, or 4 tablets per day. All tablets will be enteric coated to reduce the chance of stomach upset, which sometimes occurs with ASA. These side effects of ASA include bleeding, heartburn, gastritis, and dyspepsia. Other side effects may include tinnitus, nausea and vomiting.

I understand that there is an equal chance that I will receive one of the 4 ASA doses, which will be provided in identically appearing blister packs, with 5 tablets to be taken each day (3 in the morning and 2 in the evening, with meals). Neither I nor my physicians will know which dose I have been given, but should my doctor need to know, this information will be made available.

As a patient enrolled in this study I will continue to receive medical care and while I may benefit from the increased medical supervision for this study, no benefit from the study drug can be guaranteed. This study will provide important information regarding the relative efficacy and safety of the 4 ASA doses regimens for patients undergoing carotid endarterectomy. Many patients including myself may benefit from this information.

I understand that it is important that I take the study drug each day and avoid all other sources of ASA for the 3 months of my participation in this study. While I must avoid over-the-counter products which contain ASA, I will be able to use acetaminophen for minor aches and pains, if necessary. I will check with my doctor before starting any new medicines during the study. Essential medications which I require for other medical conditions are allowed.

Following discharge from hospital after the operation I will be asked to return for follow-up

assessments at 30 days and 3 months after the operation, and will be asked to bring my study medication pacs with me. The study drug will be provided free of cost and there will be no additional medical tests or treatments required for the study beyond those required by my physicians for my operation and subsequent medical care. In the event of any medical or surgical complication I will be provided with appropriate medical treatment. However, neither free medical care nor any financial compensation for illness or injury will be provided.

All data collected for the study will be held in confidence and only used to answer the research questions posed by the investigators. I will not be identified individually in any listing or report arising from this study. When the trial is completed (approximately July 1997) I will receive a personal letter from the study investigators which will include a short description of the study findings.

I understand that my participation in this study is voluntary, that my refusal to participate will involve no penalty, compromise my medical care, or lead to loss of any benefits to which I am otherwise entitled, and that I may discontinue my participation in the study at any time without penalty or loss of benefits. I further understand that my doctor or the study investigators may decide to discontinue the study drug at any time for medical reasons or if it is in my best interest to do so. Further, any new findings which may arise during the course of this research which may relate to my willingness to continue will be provided to me.

All of my questions have been answered and I voluntarily consent to participate in this research study. If I have any further questions about this study I may contact the study coordinator or participating clinical investigator in my center listed below.

Study Coordinator _____ Telephone _____

Clinical Investigator _____ Telephone _____

I will be given a copy of this signed consent form which I have read and understood.

Print Patient's Name Patient's Signature Date

Print Name of Witness Witness Signature Date