The Carotid Occlusion Surgery Study

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The St. Louis Carotid Occlusion Study demonstrated that ipsilateral increased O₂ extraction fraction (OEF) (Stage II hemodynamic failure) measured by positron emission tomography (PET) is a powerful independent risk factor for subsequent stroke in patients with symptomatic complete carotid artery (CA) occlusion. The ipsilateral ischemic stroke rate at 2 years has been shown to be 5.3% in 42 patients with normal OEF and 26.5% in 39 patients with increased OEF (p = 0.004). In patients in whom hemispheric symptoms developed within 120 days, the 2-year ipsilateral stroke rates were 12% in 27 patients with normal OEF and 50% in 18 patients with increased OEF. Previous PET studies have demonstrated that anastomosis of the superficial temporal artery (STA) to a middle cerebral artery (MCA) cortical branch can restore OEF to normal.

The authors discuss the undertaking of a study that will test the hypothesis that STA–MCA anastomosis, when combined with the best medical therapy, can reduce ipsilateral ischemic stroke by 40% at 2 years in patients with symptomatic internal CA occlusion and Stage II hemodynamic failure occurring within 120 days after surgery. Only patients with increased OEF distal to a symptomatic occluded CA will be randomized to surgery or medical treatment. The primary endpoint will be all strokes and death occurring between randomization and the 30-day postoperative cut off (with an equivalent period in the nonsurgical group), as well as subsequent ipsilateral ischemic stroke developing within 2 years. It is estimated that 186 patients will be required in each group. Assuming that 40% of PET scans will demonstrate increased OEF, this will require enrolling 930 clinically eligible individuals.

KEY WORDS • carotid artery • internal carotid artery • revascularization • extracranial–intracranial bypass • randomized trial

Approximately 730,000 initial or recurrent strokes occur each year in the US. In 10 to 15% of patients presenting with CA territory stroke or TIA complete CA occlusion is found.2,28,38 This results in an estimated 61,000 first-ever strokes and 19,000 TIAs annually in the US that are associated with complete CA occlusion. Prevention of subsequent stroke in patients with CA occlusion remains difficult. In 12 prospective follow-up studies (mean duration 45.5 months) of angiographically documented symptomatic CA occlusion in 1261 patients, investigators found an overall annual risk of subsequent stroke of 7% and an annual risk of stroke ipsilateral to the occluded CA of 5.9%.19 These risks persist even with the use of platelet-inhibitory drugs and anticoagulant therapies.

REVIEW OF PAST REVASCULARIZATION STUDIES

In the International Study of Extracranial-to-Intracranial Arterial Anastomosis the investigators tested the usefulness of STA–MCA bypass surgery as a prophylaxis against stroke.9 The results were not encouraging despite good surgery-related outcome achieved by a skilled group of surgeons who reported a high rate of sustained bypass patency. In the 808 patients with symptomatic CA occlusion in this study, STA–MCA bypass was not effective. The results of this study were disappointing to the neurosurgery and stroke communities and, most of all, to the investigators. Based on the results of this trial, EC–IC arterial bypass was generally abandoned as a treatment for symptomatic CA occlusion. Subsequently, different groups criticized the trial on several grounds.1,6,37 The results of this EC–IC bypass study, however, have not been invalidated.

One possible valid criticism of the trial was its inability to identify and separately analyze a subgroup of patients with reduction in CPP in whom surgical revascularization might be more beneficial.6,35,41 At the time that this trial was conducted, there was no reliable and proven method for identifying a subgroup of patients in whom cerebral hemodynamic factors were of primary pathophysiological significance.
importance. The relative importance of hemodynamic and embolic factors in patients with complete CA occlusion remains unclear. These patients may suffer stroke from hemodynamic insufficiency distal to the CA occlusion or from emboli arising from several sources, including the stump of the occluded ICA in the neck, the tail of the thrombus that forms distal to the occlusion, and the contralateral CA. Treatment with antithrombotic drugs such as aspirin or warfarin is not likely to prevent hemodynamic stroke. Surgical revascularization procedures have the potential to prevent hemodynamic cerebral infarction.

A variety of indirect methods for evaluating the status of the distal cerebral vasculature have been developed to understand better the effects of proximal atherosclerotic lesions and collateral circulation on cerebral hemodynamics. The rationale for these methods is based on the compensatory responses made by the brain to progressive reductions in CPP. A fairly uniform value for the ratio between CBF and cerebral metabolism exists in all areas of the brain. Because of the resting balance between flow and metabolism, the cerebral OEF from the blood shows little regional variation. The actual value for OEF varies in individuals and from measurement to measurement within the same person, but it is approximately one third for normal individuals. Changes in CPP over a wide range have little effect on CBF. Increases in mean arterial pressure produce vasoconstriction of pial arterioles, and decreases produce vasodilation, thus altering resistance and maintaining a constant CBF. This phenomenon is known as autoregulation. These changes are accompanied by corresponding changes in intravascular CBV, with CBV increasing as CPP is reduced. Autoregulation fails when the capacity for compensatory vasodilation has been exceeded and CBF begins to decline. Evaluation of measurements of arteriovenous O₂ differences obtained in animals and humans has underscored the brain’s capacity to increase the OEF when O₂ supply is diminished due to decreasing CBF. Cerebral O₂ metabolism is now maintained by a progressive increase in OEF. Once this mechanism becomes maximal, further declines in blood flow cause disruption of normal cellular metabolism, and infarction may result.

Three basic strategies have been used to assess regional CPP in humans based on knowledge of the normal compensatory responses of the brain. In recently ischemic or infarcted brain tissue, CBF, CBV, CMRO₂, and cerebrovascular reactivity can be profoundly changed in a complex manner. The first strategy entails using paired rCBF measurements, with the initial measurement obtained at rest and the second measurement obtained after provision of a cerebral vasodilatory stimulus. Induction of hypercapnia, administration of acetazolamide, and physiological tasks such as hand movement have been used as vasodilatory stimuli. Normally, each results in a robust increase in CBF. If the CBF response is muted or absent, preexisting autoregulatory cerebral vasodilatation caused by reduced CPP is inferred. A second strategy involves either the measurement of rCBV alone or in combination with measurements of rCBF in the resting brain to detect the presence of autoregulatory vasodilatation. The third strategy relies on direct measurements of rOEF to identify patients with increased OEF as a result of impaired cerebral hemodynamics. Combining rOEF measurements with rCBV and rCBF measurements increases the information available to allow for accurate assessment of cerebral hemodynamics. Positron emission tomography measurements of rCBF, rCBV, and rOEF have been used to classify changes in regional cerebral hemodynamics into three stages. Regional CBV, the rCBV/rCBF ratio, and rOEF are all normal at normal levels of CPP (Stage 0). At milder levels of CPP reduction, the cerebral resistance vessels dilate to maintain CBF. Regional CBV is normal or mildly reduced (depending on metabolic demand), rCBV is elevated, and rOEF remains at normal levels (Stage 1). If CPP decreases to lower levels, the capacity of the cerebral resistance vessels to dilate and maintain blood flow is exceeded, and rCBF begins to decline. Regional CBV, the rCBV/rCBF ratio, and rOEF all increase. The ability of the brain to increase the extraction of O₂ from the blood, which is reflected by the increased rOEF, enables the brain to maintain O₂ use at normal levels (Stage 2), which reflects a more severe decrease in CPP (Fig. 1).

The impact of cerebral hemodynamics on the pathogenesis and treatment of stroke has been assessed using several different methodologies. The strongest evidence for an association between cerebral hemodynamic impairment and stroke has been provided by the SLCOS. This was a blinded prospective study conducted to test the hypothesis that Stage 2 hemodynamic failure (increased OEF) in the cerebral hemisphere distal to complete CA occlusion was an independent predictor of the subsequent risk of stroke in symptomatic medically treated patients. Inclusion criteria were occlusion of one or both common CAs or ICAs as demonstrated by angiography or MR angiography in patients with transient ischemic neurologic deficits (including transient monocular blindness) or mild-to-moderate neurologic deficits (stroke) in the territory of the occluded CA. Positron emission tomography measurements of CBF, CBV, CMRO₂, and OEF were undertaken. Patients with left-to-right OEF ratios in the MCA territory outside the normal range were categorized as having Stage 2 hemodynamic compromise in the cerebral hemisphere with higher OEF. These categorizations were made without knowledge of the side of the CA occlusion or of the clinical course after the initial PET study was obtained. No information regarding the results of PET scanning was provided to the patients, treating physicians, or investigator responsible for determining endpoints. The primary end-point was subsequent ischemic stroke, defined clinically as a neurologic deficit of presumed ischemic cerebrovascular cause lasting longer than 24 hours in any cerebrovascular territory. Secondary endpoints were ipsilateral ischemic stroke and death. All living patients were followed for the duration of the study. Patients were divided into two groups: those with stage 2 hemodynamic compromise (Fig. 1) and those with normal (symmetrical) OEF. Comparison of 17 baseline risk factors and subsequent medical treatment between the two groups was performed. Successful initial data collection and PET measurement were performed in 81 patients who were enrolled in the study. Stage 2 hemodynamic failure (increased OEF) in one hemisphere was documented in 39 patients, and no such failure was found in 42. In all 39 patients with Stage 2 hemodynamic failure, the hemisphere with increased OEF was ipsilateral to the occluded CA. There were no significant differences between the two
groups in baseline risk factors or subsequent medical treatment. Arteriographic demonstration of the collateral circulation did not permit differentiation between the two groups.

The mean follow-up duration of the patients was 31.5 months. Fifteen total and 13 ipsilateral ischemic strokes occurred during the follow-up period. There were no hemorrhages. In the 39 Stage 2 patients, 12 total and 11 ipsilateral strokes occurred. In the 42 patients with normal OEF, there were three total and two ipsilateral strokes. The Kaplan–Meier estimates for the risk of subsequent stroke at 1 and 2 years are given in Table 1. The risk of all ischemic strokes in symptomatic Stage 2 patients was significantly higher than that in those with normal OEF (p = 0.005 and p = 0.004, respectively). Twelve deaths occurred during the follow-up period. Ten deaths were caused by nonstroke-related factors, and two deaths resulted from large cerebral infarctions ipsilateral to a symptomatic occluded ICA. Both stroke-related deaths occurred in patients with increased OEF. There were six deaths in each group. No significant difference in the risk of mortality was demonstrated (p = 0.942). In the univariate analysis of the relation between patient characteristics and subsequent medical treatment, only younger age and Stage 2 hemodynamic failure were significant predictors of all strokes. Both variables remained significant in the multivariate analysis.

Investigators in a Japanese study also demonstrated that PET measurements of OEF can predict subsequent stroke in patients with symptomatic cerebrovascular disease. Yamauchi and coworkers performed PET measurements in 40 medically treated patients with symptomatic occlusion or intracranial stenosis of the ICA or MCA systems. Carotid artery occlusion was demonstrated in 30 patients. Cases were divided into two categories based on the mean hemispheric value of OEF in the symptomatic cerebral hemisphere. Seven patients with OEF greater than 53.3% (the 95% confidence intervals obtained in 10 healthy individuals) were considered to have increased OEF; the remaining 33 were considered to have normal OEF. At 1 year after the PET studies, stroke had developed in five of seven patients with increased OEF. Four strokes were ipsilateral and one was contralateral. A stroke occurred in four of 33 patients with normal OEF; two strokes were ipsilateral and two were contralateral. After the 1st year of follow up, one ipsilateral stroke and one contralateral stroke occurred, both in patients with normal OEF. This corresponds to a 2-year ipsilateral stroke rate of 57% in the high OEF group and 15% in the normal OEF group. This difference was significant for total (p = 0.0002) and
ipsilateral stroke (p = 0.002). Multivariate analysis revealed that absolute OEF and recurrent symptoms were the only significant independent predictors of subsequent stroke.

In several laboratories PET has been used to demonstrate postoperative improvement of cerebral hemodynamics after STA–MCA bypass.4,5,14,21,24,30,31,34 In patients with Stage 2 hemodynamic failure (increased OEF), EC–IC bypass returns hemispheric OEF ratios to normal.27 Surgical procedures that improve the SLCOS were poor and comparable with those reported using impaired cerebral hemodynamics in the selection of patients for EC–IC bypass to prevent stroke thus remains unproven at this time.

The results of medical treatment of Stage 2 patients in the SLCOS were poor and comparable with those reported for medically treated patients harboring symptomatic severe CA stenosis.27 Surgical procedures that improve cerebral hemodynamics such as EC–IC bypass surgery would be a logical treatment for these patients. In the absence of an empirical trial, however, it cannot be assumed that the morbidity and mortality attendant on surgery would be outweighed by any subsequent reduction in stroke risk. The large multicenter randomized trial of EC–IC bypass surgery conducted between 1977 and 1985 showed no benefit of surgery related to preventing subsequent stroke.9 At the time that this trial was conducted, there was no reliable and proven method for identifying a subgroup of patients in whom cerebral hemodynamic factors were of primary pathophysiological importance. It has been established that such a subgroup can be identified and, furthermore, that they are at high risk for subsequent stroke when treated only medically. It is appropriate to perform a new trial of EC–IC bypass surgery restricted to patients with symptomatic CA occlusion and Stage 2 (increased OEF) impairment of cerebral hemodynamics.

THE COSS

The goal of the trial is to test the hypothesis that STA–MCA anastomosis, when combined with the best medical therapy, can be reduced by 40%, despite perioperative stroke and death, subsequent ipsilateral ischemic stroke (fatal and nonfatal) at 2 years in patients with recent (≤120-day) symptomatic ICA occlusion and ipsilateral increased OEF measured by PET. The hypothesis will be tested by conducting a nonblinded, controlled trial in 372 patients randomized equally to surgical or nonsurgical treatment. Only patients with impaired hemodynamics in the cerebral hemisphere ipsilateral to the CA occlusion will be randomized.

Before proposing a PET-based clinical trial based to select patients with symptomatic CA occlusion for EC–IC bypass, a thorough examination of cost effectiveness was performed.7 A Markov chain model was created to compare the costs and effectiveness of medical treatment alone with PET screening followed by EC–IC bypass (if OEF was elevated) in patients with symptomatic CA occlusion. The incremental costs per incremental QALY gained were calculated. The cohort used in this analysis consisted of a high-risk group of 45 patients with increased OEF and recent (within 120 days) symptoms of cerebral hemispheric ischemia identified by retrospective subgroup analysis from the STLCOS. In the base-case analysis, the count-based OEF threshold determined a priori from the range of normal values was used. In subsequent analyses, different OEF thresholds were evaluated to identify the optimal one in terms of cost effectiveness. Based on this analysis, it was believed that screening of patients with CA occlusion who exhibited hemispheric symptoms within 120 days and, in those with increased OEF, who then underwent EC–IC bypass would prolong quality-adjusted survival by 50 QALYs/10 years/100 patients at a cost of $19,600 per QALY gained compared with medical therapy alone. This cost per QALY is considered to be highly cost effective. A more specific OEF threshold determined from post hoc data analysis identified a very high-risk group, resulting in a gain of 49 QALYs/10 yrs/100 patients at a cost savings of $11,000 per patient. This more specific OEF threshold was used in the design of the COSS.

The major patient inclusion criteria include the following. 1) A TIA or mild-to-moderate permanent ischemic neurological deficit (modified Barthel Index ≥ 12/20) in the hemispheric CA territory appropriate to the occluded CA (within 120 days prior to PET). 2) Increased OEF in the symptomatic cerebral hemisphere ipsilateral to the occluded CA (PET O\(^{15}\) O/H\(_2\)O count–based ratio image with ipsilateral-to-contralateral OEF ratio > 1.13) (Fig. 1). 3) Intraarterial arteriography demonstrating the following: occlusion of oneICA; less than 50% stenosis of the contralateral extracranial ICA; and extra- and intracranial vessels suitable for STA–MCA anastomosis.

Eligibility for PET scanning will be based on fulfillment of clinical entry criteria and the presence of unilateral CA occlusion with less than 50% contralateral extracranial ICA stenosis evidenced on Doppler ultrasonography, MR angiography, computerized tomography angiography, or intraarterial arteriography. If PET scanning demonstrates findings consistent with criteria for ipsilateral increased oxygen extraction, then arteriographic criteria must be met prior to randomization. Thus, intraarterial arteriography is required prior to randomization to document CA occlusion, less than 50% contralateral extracranial ICA stenosis and both extracranial and intracranial arteries suitable for anastomosis. Prior to PET scanning, a decision will be made whether supplemental arteriogra-

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TABLE 1

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<thead>
<tr>
<th>Kaplan–Meier estimates of stroke risk for symptomatic patients*</th>
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<tr>
<td>Group</td>
<td>Total</td>
<td>W/ Increased OEF</td>
<td>W/ Normal OEF</td>
</tr>
<tr>
<td>no. of patients</td>
<td>81</td>
<td>39</td>
<td>42</td>
</tr>
<tr>
<td>1 yr</td>
<td>7.7%</td>
<td>13.2%</td>
<td>2.4%</td>
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<td>2 yrs</td>
<td>19.0%</td>
<td>29.2%</td>
<td>9.0%</td>
</tr>
<tr>
<td>ipsilateral strokes</td>
<td>1 yr</td>
<td>6.4%</td>
<td>10.6%</td>
</tr>
<tr>
<td>2 yrs</td>
<td>15.8%</td>
<td>26.5%</td>
<td>5.3%</td>
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* From Grubb, et al., used with permission.
phy will be necessary either because it has not been performed or because the existing study is inadequate to provide the necessary information. Supplemental arteriography will be undertaken as part of COSS only if the PET study meets criteria for increased OEF. After consent is obtained, all patients will be instructed to take aspirin (81–325 mg per day) and to discontinue the use of any other antithrombolytic therapy (specifically oral anticoagulant agents, ticlopidine, clopidogrel and diprydamole) until the 30 to 40–day follow-up visit. After this time, the need for antithrombolytic therapy will be determined by the physicians caring for the patient.

Patients randomized to surgery will undergo STA-MCA bypass as soon as possible. Standard surgical techniques for anastomosis of one branch to a cortical branch of the MCA will be used. All randomized patients will receive the best available medical treatment with antithrombolytic agents and risk-factor intervention to prevent subsequent stroke. All surgery-treated patients will be seen 30 to 40 days postoperatively. Patients not undergoing surgery will be seen 40 to 50 days after randomization. All surgery-treated patients will undergo PET scanning 30 to 40 days after surgery to document reversal of hemodynamic abnormalities. All individuals will be seen at 3-month intervals for the duration of the study.

Primary outcome will be based on the occurrence of ipsilateral ischemic stroke within 2 years of randomization. In the bypass group, outcome will be the occurrence of all strokes or death occurring between randomization and a 30-day postoperative time point, as well as the subsequent occurrence of ipsilateral ischemic stroke. For the nonbypass group, outcome will be the occurrence of all strokes or death during the aforementioned period, as well as the subsequent occurrence of ipsilateral ischemic stroke.

Secondary outcomes will also include all stroke, disabling stroke, fatal stroke, death, Rankin Scale score, National Institutes of Health Stroke Scale score, modified Barthel Index, and Stroke Specific Quality of Life Assessment.

The initial design of the study requires enrollment of 930 clinically eligible patients for PET scanning—yield 372 patients with increased OEF for randomization, half to surgery and half to nonsurgical therapy. Given our current estimates of the primary event rates, this will yield 90% power for a 5% level two-sided test to detect a 40% decrease in the rate of the primary outcome in favor of the surgery arm.

**CONCLUSIONS**

Increased OEF (Stage II hemodynamic failure) measured by PET scanning is a powerful, independent risk factor for subsequent ipsilateral stroke with symptomatic complete occlusion of the ICA. An STA–MCA anastomosis can restore OEF to normal level in patients with ICA occlusion. The COSS will test the hypothesis that STA–MCA anastomosis when combined with the best medical therapy can reduce by 40% subsequent ipsilateral ischemic stroke at 2 years in patients with symptomatic ICA occlusion and Stage II hemodynamic failure occurring with 120 days.

**Appendix I**

**Inclusion and Exclusion Criteria**

**A) Inclusion criteria**

1. Vascular imaging studies demonstrating occlusion of one ICA.
2. Vascular imaging studies demonstrating less than 50% stenosis of the contralateral extracranial ICA.

(Note: The two aforementioned inclusion criteria may be demonstrated using any vascular imaging modality (that is, Doppler ultrasonography, MR angiography, computerized tomography angiography or intraarterial arteriography. Additionally, validation of sensitivity and specificity of nonarteriographic modalities compared with arteriography is not required because all participants must have undergone catheter arteriography to determine final eligibility.)

3. A TIA or ischemic stroke in the hemispheric CA territory of the occluded CA.
   a) This is a clinical diagnosis based on all available data not requiring confirmation by neuroimaging. Patients with TIA or infarction restricted to the retina only are not eligible, but those with combined retinal and hemispheric CA territory syndromes will be eligible. In patients with hemisensory or hemimotor signs or symptoms, including a single limb, specific hemispheric signs or symptoms (for example, aphasia) will not be required for inclusion, but absence of cerebellar and brainstem signs or symptoms will be required.
   b) Patients who have previously undergone endarterectomy for stenosis of the ipsilateral external carotid or contralateral ICA are eligible whether or not they experience recurrent symptoms.
   c) Patients who have undergone carotid endarterectomy for symptomatic CA stenosis in whom a postoperative CA occlusion develops but who experience no further symptoms after surgery are not eligible unless additional symptoms occur.
4. Most recent qualifying TIA or stroke must have occurred within 120 days prior to the performance date of PET.
5. Modified Barthel Index score greater or equal to 12/20.
6. Language comprehension intact, motor aphasia mild or absent such that effective communication is possible.
7. Age ranging between 18 and 85 years.
8. Competent to give informed consent.
9. Legally an adult.
10. Geographically accessible and reliable for follow-up examinations.

**B) Exclusion criteria**

1. Nonatherosclerotic CA disease. (The intent is to include only those with atherosclerotic CA occlusion. All other nonatherosclerotic conditions (for example, moyamoya disease, fibromuscular dysphasia, CA dissection, arteritis, radiation-induced vasculopathy such as that occurring after irradiation for neck cancer) are excluded. These entities are given as examples, and not as an all-inclusive list.)
2. Blood dyscrasias including the following conditions only: polycythemia vera; essential thrombocytosis; and sickle cell disease. (This is an all-inclusive list. The following conditions are not exclusions: anticardiolipin antibodies, lupus anticoagulant, proteins S or C deficiency, antithrombin III deficiency, Factor V Leiden or other causes of activated protein C resistance, and prothrombin gene mutations.)
3. Known heart disease likely to cause cerebral ischemia (echocardiography is not required) including the following conditions only: atrial fibrillation, prosthetic valve(s), infective endocarditis, left atrial or ventricular thrombus, sick sinus syndrome, myxoma, and cardiomyopathy with ejection fraction less than 25%. (This is an all-inclusive list. The following conditions are not exclusions: patent foramen ovale or atrial septal aneurysm.)
4. Other nonatherosclerotic conditions likely to cause focal cerebral ischemia.
5. The following medical conditions: cancer (other than skin), renal failure (blood urea nitrogen and/or creatinine > twice normal upper limit), congestive heart failure, myocardial infarction within 6 months, liver disease, and pulmonary disease constituting an anesthetic risk.
6. Any condition likely to lead to death within 2 years.

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7) Other neurological disease that would confound follow-up assessment.
8) Pregnancy.
9) Subsequent planned cerebrovascular surgery that might alter cerebral hemodynamics or stroke risk. (This includes contralateral internal or common carotid endarterectomy or angioplasty, ipsilateral external CA endarterectomy or angioplasty, CA stump closure, vertebral or basilar artery angioplasty, any arterial grafting procedures to the CA or vertebral arteries.)
10) Any condition that in the participating surgeon’s judgment makes the patient an unsuitable surgical candidate.
11) Concurrent participation in any other experimental treatment trial.
12) Participation within the previous 12 months in any experimental study that included exposure to ionizing radiation.
13) Acute, progressing, or unstable neurological deficit (neurological deficit must be stable for 72 hours prior to of PET scanning).
14) Allergy to iodine or radiographic contrast media if supplemental arteriography is required.
15) Allergy to aspirin.
16) Medical indication for treatment with antiplatelet drugs, ticlopidine, clopidogrel, or dipyridamole such that these medications cannot be replaced with aspirin for 1 month after enrollment. (Note: patients with any of the medical conditions specified in exclusion Criteria 17 through 20 can become eligible if the exclusion criterion no longer applies within 120 days of onset of the most recent qualifying event.)
17) Uncontrolled diabetes mellitus (fasting blood glucose > 300 mg%/16.7 mmol/l).
18) Uncontrolled hypertension (systolic BP > 180, diastolic BP > 110).
19) Uncontrolled hypotension (diastolic BP < 65).
20) Unstable angina.

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