Aggrenox Prevention of Access Stenosis
STUDY PROTOCOL

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1. BACKGROUND AND RATIONALE FOR STUDY

According to the most recent statistics from the USRDS nearly 200,000 patients were on hemodialysis in the US in 1997 (1). The number of patients on hemodialysis has doubled over the last 8 years and continues to grow at an increasing rate (1). This increase has occurred across all strata of age, race and underlying renal disease but has been greatest in the older population and for patients with diabetes (2). The increasing age and comorbid conditions have engendered a number of problems but none as vexing as the increasing problem of vascular access failure. A well functioning vascular access is essential to providing adequate hemodialysis. Yet vascular access failure is the single biggest cause of morbidity and a major expense in providing care to hemodialysis patients (3-5). Based on data from the USRDS, the overall primary access survival defined as the time to first thrombosis, thrombolysis, angioplasty or revision for all arteriovenous accesses combined (both native and prosthetic graft fistulas) in the U.S. is 53% at 1-year (6). The associated expenses are also high (4, 5, 7). Access procedures are the single greatest expense submitted to Medicare for hemodialysis patients (5). A review of the Medicare hemodialysis database from 1984-86 indicated that over 15% of all hospitalizations for hemodialysis patients were attributable to a vascular access problem (4). The costs to care for access related problems have been recently estimated to be between 8-11% of total Medicare ESRD spending or between $0.7-1 billion per year (5). Clearly, this is a problem of major importance for the hemodialysis patient and the health care system.

1.1 Native AV Fistulas (AVF) Versus Synthetic AV Grafts (AVG)

Numerous studies have shown that the established native AVF has a better long-term survival and fewer access related procedures than the AVG (3, 4, 6, 8-11). Yet, the prevalence of the AVG has been increasing and the overall use of an AVG now substantially exceeds that of a native AVF in the U.S. (4, 6, 12, 13). The reasons for this increase in the use of an AVG are not entirely clear and probably multifactorial (12). The preferred access is the lower arm radiocephalic AVF (LAF) (3). However, the LAF is more difficult to create and often fails to mature particularly in older patients, women and those with significant underlying vascular disease such as seen with diabetes (4, 14-16). This has led some investigators to question whether the LAF is the best hemodialysis access for many of our current patients (14). One alternative that is receiving more attention is the upper arm native AVF (UAF) (3, 17-19). The UAF has a better survival, a low rate of infections and is more cost effective than an AVG (3, 11, 17, 18, 20). However, the UAF is avoided by many dialysis centers because of concerns over difficulty in cannulating the fistula and the higher flow rate leading to high output heart failure and distal arm steal syndromes (3).

The Dialysis Access Consortium (DAC) strongly endorses the use of a native fistula as the preferred access and has embarked on a companion trial to deal with the problem of the high early failure rate. Nevertheless, even in hemodialysis units with an aggressive policy of native fistula placement, a graft is required in up to one third of all accesses placed. With an aging hemodialysis population and the associated increase in underlying vascular disease the AVG will continue to be an important means of providing a hemodialysis access. Moreover, studies to address and prevent access stenosis (the underlying cause of access failure) in patients with an AVG may have broader application to access failure in native fistulas as well as vascular disease in general.

1.2 Access Stenosis the Primary Etiology for Vascular Access Failure

The underlying etiology for access failure is nearly always stasis and thrombosis due to the presence of access stenosis (3, 9, 10, 16, 21-25). In an AVG, over 90% of all stenotic lesions are in the vein downstream of the graft with the remaining lesions found within the body of the graft or at the arterial anastomosis (21-25). Stenosis in native AVF also occurs most commonly in the vein just

downstream of the anastomosis (22). The stenotic lesion has been characterized pathologically as a dense neointimal hyperplasia (26-29). Histochemically, the neointimal thickening consists predominantly of vascular smooth muscle cells and associated extracellular matrix material (26-29). Prominent capillary infiltration (angiogenesis) is found throughout the neointima and particularly at the intima-media boundary (27, 29). Macrophages are found in association with capillaries and lining the surface of the graft material (27-29). Positive staining for smooth muscle mitogens PDGF and FGF as well as the endothelial mitogen VEGF is abundant within the neointima (29). Increased cellular proliferation is a well-established characteristic of the lesion and is present within the neointima, media and adventitia (27-29). Proliferation of smooth muscle cells is frequently associated with proliferation of nearby endothelial cells throughout the lesion (27-29). The observed close association of endothelial and smooth muscle proliferation in the neointima raises the intriguing possibility that proliferating endothelial cells might stimulate rather than inhibit the proliferation of smooth muscle cells (27, 28, 30-32). In contrast to the pathology of advanced atherosclerotic lesions, a lipid core and fibrous cap are not seen (27-29). These findings document that the vascular access stenosis is a dense lesion characterized by a high rate of proliferation of both vascular smooth muscle and endothelial cells along with abundant extracellular matrix material.

1.3 Pharmacological Approaches to Preventing Access Stenosis

The available evidence suggests that prevention of neointimal hyperplasia and the resulting vascular access stenosis is the key to decreasing access failure. Table 1.1 lists some of the currently available pharmacological agents that have been considered for preventing access failure (33). However in prospective studies published to date, only dipyridamole has been shown to prolong graft survival (34). In a small study, dipyridamole (Persantine, Boehringer-Ingelheim) but not aspirin was effective in preventing access thrombosis in newly created grafts (34). After 18 months, thrombosis occurred in 17% of patients on dipyridamole, 50% on aspirin, 23% on dipyridamole plus aspirin and 32% of those on placebo (34). These results suggested that dipyridamole was acting by another mechanism other than as an antiplatelet or antithrombotic agent. Subsequent studies demonstrated that dipyridamole and aspirin had opposite effects on smooth muscle cell proliferation in vitro (35, 36). Dipyridamole inhibited growth factor-stimulated proliferation while aspirin enhanced proliferation (35, 36). Similar results have been seen in an animal model of restenosis *in vivo* (37). These studies suggest that dipyridamole might prevent access failure by inhibiting the vascular smooth muscle cell proliferation that leads to neointimal hyperplasia and access stenosis. One possible mechanism by which dipyridamole might inhibit vascular smooth muscle cell proliferation is via an increase in adenosine. Dipyridamole inhibits adenosine uptake and has been shown to inhibit vascular smooth muscle cell proliferation via adenosine A2B receptors (38-40). Dipyridamole also inhibits phosphodiesterase activity and the resulting increase in cGMP or cAMP levels might also contribute to inhibiting vascular smooth muscle cell proliferation (41, 42). However, the exact cellular mechanism whereby dipyridamole or adenosine works to inhibit vascular smooth muscle cell proliferation is not known (40, 43). In contrast to this prospective study, a letter reporting a retrospective analysis of new graft survival in patients on a variety of medications found no effect of dipyridamole but details of the analysis are scanty and the weight of the evidence is poor (44).

TABLE 1.1: Some Clinically Available Drugs for Prevention of Access Failure

Dipyridamole
Fish oil
HMG CoA reductase inhibitors
ACE inhibitors
Angiotensin AT1 receptor blockers
Heparinoids / Pentosan phosphate
Sirolimus (Rapammune)
Trapidil
Tranilast
Ticlopidine

No other prospective analysis of dipyridamole for vascular access failure has been published to date. However, in discussions with Boehringer Ingelheim it came to light that an unpublished

randomized, placebo-controlled trial of long acting dipyridamole (ASASANTIN Retard) and low dose aspirin was done between 1986 and 1989 in Germany (unpublished data, Boehringer Ingelheim). The study randomized 903 subjects to either the combination of aspirin (25 mg) plus ASASANTIN Retard (200 mg) twice a day (451 subjects) or matching placebo (452 subjects) starting 2 days prior to access creation. The type of access was not specified. However, based on discussions with medical personnel who worked in the dialysis unit at the time of the study and from a review of the literature on access procedures done in Germany at that time, it is likely that most of the accesses placed were native fistulas. The subjects were followed for up to 18 months on study medication and the primary outcome was primary unassisted patency. The groups appeared to be well matched for baseline covariates. However, there was no difference in the primary outcome between the two groups. By intention-to-treat analysis, the primary endpoint was reached in 19.7% of subjects on study medication verses 20.8% of subjects on placebo. The duration of access survival was 2.98 years for both groups. A concerted effort was made to determine whether any patients with grafts were enrolled into the study and whether a subgroup analysis of these patients was performed but no data was available on this important issue.

The results of this unpublished study do not exclude the possibility that dipyridamole could be effective to prevent access failure in arteriovenous grafts. First, the biology of access failure in a native fistula may be different than for a graft. In contrast to a native fistula, using synthetic graft material leads to activation of coagulation, releases cytokines and growth factors and induces a foreign-body reaction at the anastomosis site. All of these events may play a significant role in stimulating the venous myointimal hyperplasia that leads to graft failure. Second, the rate of primary access failure (~20% over 18 months) and patient mortality (8% per year) in this earlier study are markedly lower than the expected rate of primary failure and patient survival in the present study (over 50% and 16% per year, respectively). This suggests that there is a significant difference in the two patient populations. One reason for this difference may be the lower number of diabetic patients (25%) in the earlier unpublished study compared to that currently seen in the U.S. dialysis population. These observations suggest that a trial of dipyridamole to prevent access failure in grafts is still warranted.

On a broader scale, the combination of dipyridamole plus aspirin has been reported to decrease the incidence of late stenosis developing in veins used for coronary bypass grafts (45, 46). In the study by Chesebro et al. the combination of dipyridamole plus aspirin reduced the percentage of late graft occlusions from 27% to 16%. Dipyridamole has also been shown to be effective as a single agent in the secondary prevention of stroke suggesting that it has efficacy when used alone in reducing morbidity in patients with established vascular disease (47). Taken together, the weight of published evidence argues that dipyridamole represents the current best choice for pharmacological therapy to prevent access failure. However, the only published study to date in dialysis grafts was small and underpowered and a larger clinical trial of dipyridamole is clearly needed.

1.4 Selection of Aggrenox for the Study

In the previous published trial, dipyridamole was given as Persantine (Boehringer-Ingelheim) 75 mg by mouth three times a day (34). The therapy was well tolerated with only modest side effects. However, giving dipyridamole three times a day may reduce compliance. More importantly, it has been found that absorption of immediate release dipyridamole is variable and depends on an acid environment in the stomach (106). Between 10-30% of the elderly population has hypochlorhydria (104, 105). Moreover, many dialysis patients are on a proton pump inhibitor that will impair absorption of dipyridamole (106). An extended release preparation of dipyridamole that contains a tartaric acid solubilizer to enhance absorption is now available in the U.S. in the form of Aggrenox (Boehringer-Ingelheim) (48, 49). Aggrenox contains 200 mg of extended release dipyridamole and 25 mg of immediate release aspirin per capsule and is taken twice a day by mouth. Pharmacokinetic studies have shown that Aggrenox gives a more sustained plasma level of dipyridamole with a higher trough level and 50% greater bioavailability in persons with low gastric pH than that attained with Persantine (personal communication, Boehringer-Ingelheim). The higher sustained level of

dipyridamole is likely to be important to maximize the ability of dipyridamole to inhibit vascular smooth muscle cell proliferation (50). The enhanced bioavailability should reduce intersubject variability and enhance overall drug efficacy. The 25 mg of aspirin in Aggrenox provides the minimal dose of aspirin required to produce over 90% inhibition of platelet cycloxygenase (personal communication, Boehringer-Ingelheim). Moreover the 8:1 (wt:wt) ratio of dipyridamole to aspirin present in Aggrenox has been shown to inhibit thrombus formation in hamster skin fold venules better than the same dose of dipyridamole with higher doses of aspirin (personal communication, Boehringer-Ingelheim). This effect was demonstrated clinically in the European Stroke Prevention Study in which Aggrenox was found to be significantly better than either 25 mg bid of aspirin or 200 mg bid of extended release dipyridamole for the secondary prevention of stroke (47).

Based on the results of Sreedhara et al., one potential concern for using Aggrenox is the possibility that aspirin could impair the therapeutic effectiveness of dipyridamole (34). The adverse result with aspirin in that study was unexpected and the biological basis for the potential adverse effect of aspirin is unknown. However, the dose of aspirin contained in Aggrenox (25 mg bid) is much lower than the dose of aspirin (325 mg qd) used by Sreedhara et al (34). This small dose of aspirin does not impair the antiproliferative effects of dipyridamole in vitro (Himmelfarb, personal communcation). Moreover, the combination of dipyridamole and 325 mg of aspirin used in the study by Sreedhara et al. was better than placebo and not substantially worse than dipyridamole alone (34). Finally, a recent abstract from the DOPP Study reported that treatment with aspirin or antiplatelet agents improved secondary graft patency by about 25% (Young et al., J. Am. Soc. Nephrol. 12:307A, 2001). Taken together, these results imply that the low dose of aspirin in Aggrenox should not impair the effect of dipyridamole and may even improve access outcomes for some patients with grafts.

A second concern is that the aspirin component of Aggrenox might partially unmask the study blind due to increased difficulty with hemostasis at the end of dialysis. However, patients who receive Aggrenox or placebo at the time of receiving a new access will not have a baseline comparison to discern whether the study drug has altered hemostasis. Moreover, aspirin is commonly used in ESRD patients and this will tend to obscure any noticeable difference between the study patients on Aggrenox and the general hemodialysis population. A sustained release form of dipyridamole without aspirin (i.e., Persantine Retard, Boehringer-Ingelheim) is not currently available in the United States and is not likely to be made available for this study. Therefore, due to the advantages of improved compliance, more reproducible bioavailability and higher dipyridamole levels the Aggrenox formulation of dipyridamole is planned for this study.

1.5 Toxicities of Aggrenox

Dipyridamole and aspirin are widely used medications with well-characterized side effect profiles. Dipyridamole is a weak antiplatelet agent and does not significantly increase the risk of bleeding over aspirin alone (48, 49). However, dipyridamole blocks adenosine uptake and does increase the risk for adverse reactions, including hypotension and shortness of breath during adenosine infusion (e.g. for cardiac stress testing). The side effects of Aggrenox are similar to those of the two individual components and include increased risk of bleeding, gastrointestinal disturbances and headache (48, 49). The major adverse effect of Aggrenox is bleeding. In the European Stroke Prevention Study 2 (ESPS2) approximately 1650 patients with a prior history of stroke were randomized to one of four treatment groups: 1) placebo, 2) 50 mg/day aspirin, 3) dipyridamole, or 4) Aggrenox (47). Aggrenox was shown to decrease the combined risk of stroke or death significantly more than that of either aspirin or dipyridamole alone (47). Headache and gastrointestinal disturbances were the most common side effects occurring in 38.1% and 32.7% of patients on Aggrenox compared to 32.4% and 28.1% of patients on placebo, respectively (47). The rates of bleeding events and total mortality over two years follow-up in the ESPS2 were as follows:

Type of Event	Placebo	Aspirin	Dipyridamole	Dipyridamole + Aspirin
All bleeding	74 (4.5%)	135 (8.2%)	77 (4.7%)	144 (8.7%)

events				
Severe or fatal bleeding events	7 (0.4%)	20 (1.2%)	6 (0.4%)	27 (1.6%)
Intracranial bleeds	14 (0.8%)	16 (1.0%)	11 (0.7%)	16 (1.0%)
Fatal bleeds	2 (0.1%)	1 (0.06%)	2 (0.1%)	4 (0.2%)
Total mortality	202 (12.2%)	182 (11.0%)	188 (11.4%)	185 (11.2%)

Severe bleeding was defined as a bleeding event that required a transfusion. This data indicates that the risk of bleeding is primarily associated with the aspirin and that addition of dipyridamole does not substantially increase the risk of bleeding over aspirin alone (47). There was no statistically significant difference between the rate of intracranial bleeds, fatal bleeds or overall death rate in patients treated with aspirin or aspirin plus dipyridamole compared to control This study suggests that Aggrenox is likely to increase the rate of serious bleeds by 2-4-fold over control and that this increase is due to the aspirin. However, the rate of intracranial or fatal bleeds as well as overall mortality is not expected to be statistically increased by the use of Aggrenox.

A large literature exists for the use of antiplatelet agents for primary and secondary prevention of arterial thrombosis and this was reviewed to determine whether the risk for fatal or intracranial bleeds was increased by aspirin. A recent meta-analysis comparing aspirin or warfarin to placebo for the primary prevention of ischemic cardiac events revealed that 0.22% of 28,636 patients in the antiplatelet arms developed intracranial bleeds, as compared to 0.17% of 28,654 placebo patients (Odds ratio = 1.4, 95% CI: 0.9 to 2.0; [Clinical Evidence, Issue 5, June 2001 (ed. Stuart Barton) BMJ Publishing Group, pp 82-83 and 92-93]). One of the trials included in the meta-analysis was the Hypertension Optimal Treatment (HOT) study which randomized 18,790 patients to either 75 mg of aspirin a day or placebo for an average follow-up of 3.8 years (107). The HOT study reported that fatal bleeds occurred in 7 of 9399 subjects in the aspirin group and 8 of 9391 subjects on placebo. Non-fatal major bleeds were increased in the aspirin group (129 compared to 70 on the placebo) and distributed as follows:

Bleeding Complications in the HOT Study		
	ASA Group (n=9399)	Placebo (n=9391)
Gastrointestinal	72	34
Cerebral	12	12
Nasal	22	12
Other	23	12
Total	129	70

Overall mortality in the HOT study was numerically but not statistically lower in the aspirin group compared to the placebo group (3.0% verses 3.2%). These studies indicate that most of the serious bleeding episodes in the ASA group are due to gastrointestinal hemorrhage with no significant increase in fatal or intracranial hemorrhage.

The recent VA cooperative trial studying antiplatelet agents to prevent graft thrombosis found that the annual rate of serious hemorrhage was 1-1.5% in hemodialysis patients on placebo (personal communication, James Kaufman). Hence, the baseline rate of serious bleeding events in hemodialysis patients will likely be higher than that observed in the ESPS2 or primary prevention studies listed above. Aspirin has also been shown to prolong bleeding time more in patients with end stage renal disease compared to normal controls (110). These results raise concern that the risk of serious bleeding with aspirin might be greater in hemodialysis patients.

There are very few published studies of aspirin in hemodialysis patients. The few studies that are available do not suggest that the increased risk of serious bleeding with aspirin in hemodialysis patients will be any more serious or frequent than that seen in the ESPS2 or HOT trials (34, 111-113). For instance in the study by Sreedhara et al., the risk of bleeding in patients treated with either aspirin

or aspirin plus dipyridamole was about 2-fold more than placebo (34). Additional information regarding the risk of Aggrenox in hemodialysis patients comes from the unpublished study done in Germany in 1986-1989 that was cited above (unpublished results, Boehringer Ingelheim). This study used a combination of aspirin and extended release dipyridamole equivalent to Aggrenox. Bleeding led to discontinuation of study medication in 38 of 451 patients (8.4%) on study medication and 23 of 452 patients on placebo (5.0%). No patients on study medication were reported to have died from bleeding. Gastrointestinal disorders were reported as a cause for discontinuing the medication in 53 patients (11.8%) on study medication and 36 patients (8.0%) on placebo (unpublished results, Boehringer Ingelheim). The members of the Steering committee also surveyed their affiliated dialysis units and found that about 30% of current hemodialysis patients are taking aspirin (personal communication). This suggests that in clinical practice the risk of aspirin is felt to be acceptable for many current dialysis patients. The addition of the small dose of aspirin in Aggrenox is not expected to increase the risk of bleeding in patients already on aspirin. The main increased risk of bleeding will be seen in the remaining patients who are not on aspirin. Taken together, these studies suggest that the baseline risk of serious hemorrhage will be higher in hemodialysis patients but the increased bleeding risk attributable to aspirin will be the same as that seen in other studies.

There could also be a benefit of using aspirin. Aspirin has been shown to decrease the rate of cardiovascular morbidity and mortality (107, 108). Given the high rate of cardiovascular disease in the hemodialysis population it is possible that the use of aspirin in Aggrenox might also have a beneficial effect to lower the rate of cardiovascular morbidity and mortality in this population. Indeed, the unpublished study of low dose aspirin and extended release dipyridamole done in Germany found a statistically significant 37% reduction in overall mortality in hemodialysis patients on study medication compared to control (5% annual mortality in the patients on study medication compared to 8% annual mortality in the control patients on placebo; unpublished results, Boehringer Ingelheim). The reduction in mortality was primarily due to a reduction in the number of cardiac deaths. This is even more remarkable given the low baseline rate of mortality in these patients. These results suggest that despite the increased risk of bleeding, aspirin in the form of Aggrenox may offer the exciting possibility of an overall survival benefit for patients on hemodialysis.

Considering that the risk of graft failure is much higher than the risk of a serious/fatal or moderate bleed, that the pharmcokinetics of Aggrenox are better than dipyridamole alone and the possible survival benefit of Aggrenox, it is felt that the potential benefit of Aggrenox outweighs its known risks.

1.6 Pharmacokinetics of Aggrenox in ESRD

There are no reported pharmacokinetic studies of Aggrenox in patients with ESRD or on hemodialysis. As reported above, the combination of extended release dipyridamole and low dose aspirin similar to Aggrenox has been given safely to over 450 hemodialysis patients (unpublished results, Boehringer Ingelheim). Baseline adverse events were high in the placebo group but addition of Aggrenox did not lead to an excess of adverse events compared to that expected in patients with normal renal function. Dipyridamole alone has been used in standard doses (225 mg per day) in patients with renal disease or on hemodialysis and the complications have been similar to those reported for patients with normal renal function (34, 115). Dipyridamole is highly protein bound and metabolized by the liver to the monoglucuronide that is almost exclusively excreted into bile with only minute amounts excreted in the urine (116). These studies suggest that the drug will not be readily dialyzed and that no dose adjustment is needed for patients on hemodialysis. Aspirin and its metabolites are highly protein bound. The liver also rapidly metabolizes aspirin to salicyluric acid and various glucuronide derivatives. In contrast to dipyridamole, the kidney primarily excretes these metabolites. However, protein binding of aspirin and salicyclate is decreased in uremic subjects, and the total body clearance of aspirin has been shown to be faster in uremic subjects than controls (110). The small dose of aspirin in Aggrenox (25 mg per tablet) therefore will not need to be adjusted for renal insufficiency.

1.7 Rationale for Performing the Study

Although native fistulas are preferred, there will be many patients for whom an arteriovenous graft will be the only possible vascular access. However, the median primary unassisted patency of PTFE grafts is less than 12 months and the median cumulative patency rate is less than 2 years (55, 56). Maintenance of cumulative patency requires frequent access related procedures engendering considerable discomfort for the patient and accumulating substantial costs to the health care system. The predominant cause of this high rate of failure is myointimal hyperplasia leading to stenosis and ultimately access thrombosis. Currently there is no proven therapy to ameliorate or prevent vascular access failure. However, the results from a small, randomized study have suggested that dipyridamole may be effective at reducing thrombosis of new PTFE grafts and that this effect might occur by inhibition of smooth muscle cell proliferation leading to access stenosis and failure. A large multicenter randomized placebo-controlled trial with sufficient power to detect whether dipyridamole has a clinically significant effect to prevent vascular access failure is needed. The present study is designed to test whether dipyridamole in the form of Aggrenox can prolong primary unassisted patency of newly created AV grafts. The use of standardized flow monitoring and imaging of grafts with declining flow rates will further provide important mechanistic information on the efficacy of Aggrenox to prevent access stenosis.

2. OBJECTIVES AND DESIGN

2.1 Objective

To determine whether Aggrenox (Boehringer-Ingelheim) prolongs primary unassisted patency in newly created arteriovenous grafts.

2.2 Design

The study will be a randomized double-blind, placebo-controlled multi-center trial of Aggrenox compared to placebo for the prevention of access failure in patients who receive a new arteriovenous graft. Eligible subjects will be enrolled and baseline data collected prior to the placement of a new graft. Following successful placement of the graft, subjects will be randomized with equal allocation to therapy with either Aggrenox 1 capsule twice a day or a matched placebo. For randomization, subjects will be stratified by Clinical Center and whether the graft placement is in the lower arm or at another site (e.g., upper arm or leg) and whether or not the patient is using an ACE inhibitor or angiotensin receptor blocker at enrollment. The study medication will be started within 2 days of the access surgery and continued until the primary endpoint. The primary outcome will be primary unassisted patency, defined as the time from randomization until the composite endpoint of thrombosis or any access procedure required to maintain or restore access function (subsequently referred to as the first access event). Predefined secondary outcomes include 1) the time from randomization to site failure, 2) time from randomization to death, and 3) time from randomization to the composite outcome of site failure or death. The study participants will be followed monthly to measure access flow rate and record access related complications, adverse drug reactions, hospitalizations, and medication compliance until the primary endpoint is reached. Monthly measurement of access flow rate will be used to detect a hemodynamically significant stenosis before it leads to access thrombosis. A drop in monthly access flow rate that meets pre-specified limits will trigger angiographic evaluation and repair of the access if a 50% or greater stenosis is observed. The study drug and active monitoring will be discontinued when the primary endpoint is reached. Further follow-up will be limited to determining whether total access site failure or death occurred prior to

study closeout and if so, the time of that event. It is anticipated that the study will enroll a total of 1056 subjects to have an 85% power to detect a 25% treatment effect. This projected sample size will incorporate a statistical stopping rule, which will allow the External Advisory Committee to terminate the study early if therapy with Aggrenox is proven to be effective or if it becomes clear that the null hypothesis is unlikely to be disproved.

3. ENROLLMENT, RANDOMIZATION, AND BLINDING

The study population will be drawn from patients with end-stage renal disease or chronic renal failure approaching the need for dialysis who receive a new arteriovenous access at one of the participating Clinical Centers. Since the practice patterns at each participating unit will vary, the senior investigator and study coordinator at each unit will need to develop a strategy appropriate for their own unit to identify and recruit all eligible subjects. The potential subject should be approached prior to access surgery to provide information about the study and determine eligibility for enrollment. Subjects will be given time to read the informed consent documents and ask questions about their participation in the study. If the patient meets eligibility criteria and agrees to participate s(he) will be asked to sign the informed consent document and baseline enrollment data will then be obtained. It is preferred that this visit occur prior to placement of the new graft; however, enrollment will be permitted up to two calendar days following access surgery. Patient enrollment and baseline data collection will be take place within 45 days prior to randomization. If the surgery gets rescheduled for a date more than 45 days after the initial enrollment then new baseline data will need to be obtained. If more than 90 days elapses between the time of signing the original informed consent and the access surgery, the subject will be re-apprised about the study and a new informed consent document as well as new baseline data will be obtained.

3.1 Inclusion Criteria

The inclusion criteria focus the study on relevant subjects within the study population who are likely to benefit from use of the study medication. Enrollment for this study will be open to both incident as well as prevalent adult hemodialysis patients who receive a new arteriovenous graft (either synthetic or biograft) and are able to give informed consent. The major goal of the study is to prevent the development of access stenosis. Limiting enrollment to subjects who receive a new arteriovenous graft (as opposed to including patients with prevalent grafts) maximizes the likelihood of preventing stenosis and is relevant to clinical practice. Starting Aggrenox when a new access is created mimics the protocol that worked in the study of Sreedhara et al. (34). More importantly, it maximizes the opportunity for Aggrenox to work by any of its proposed mechanisms of action, including inhibition of smooth muscle proliferation leading to the development of access stenosis or by decreasing platelet aggregation and thrombosis. The inclusion of prevalent accesses would have introduced several major problems into the study. Prevalent accesses are likely to have developed pre-existing stenoses that may be less amenable to drug therapy. In particular, prevalent accesses that have undergone a prior access procedure are less likely to respond to therapy with dipyridamole (34, 57, 58). Limiting enrollment to only those prevalent accesses that have not undergone a recent access procedure and otherwise are functioning well would decrease study feasibility by prolonging the expected event times. Overall, a negative study using prevalent accesses will fail to address the clinically important question of whether earlier initiation of Aggrenox would prevent access stenosis and failure (59-61). At this time most arteriovenous grafts are created using synthetic material (usually polytetrafluoroethylene or PTFE) placed in an upper extremity (forearm or arm). However, there is currently no evidence that the biology of access failure is any different in arteriovenous grafts composed of any other material (e.g., biografts) or placed at a site other than the upper extremity. For instance, a recent study has shown that

survival of denatured homologous vein grafts was no different than synthetic PTFE grafts (118). With regard to access location, while upper arm straight grafts tend to have a better survival than forearm grafts (of any configuration), grafts placed at other sites such as the leg appear to have a survival similar to upper arm grafts (63). There is no evidence that the response to the study drug, Aggrenox, would be affected by the type of graft material or the location of the graft. Since inclusion of all arteriovenous grafts regardless of the type of material used or the location should make the study more relevant to current practice no limitation is placed on the type or location of the graft enrolled into the study.

The inclusion criteria are:

1. Age equal or greater than that at which consent can be obtained without parental involvement (18-21 years depending on state regulations).
2. Life expectancy of at least six months.
3. Chronic renal failure with anticipated start of hemodialysis within six months of enrollment, or current dialysis-dependence.
4. A new or planned AV graft placed in any location for the purpose of hemodialysis. (Any type of graft material and any configuration of the access is acceptable).
5. The patient is expected to stay at a participating dialysis facility for at least 6 months.
6. The patient's physician(s) will allow the patient to participate.
7. Ability to give informed consent.

3.2 Exclusion Criteria

The exclusion criteria are established to exclude the following situations: 1) patients who might be at risk from participation, 2) eligible patients who do not want to be enrolled and 3) those who are unlikely to comply with the study guidelines. Note that patients who have a medical need for aspirin will not be excluded from participation in this study.

A woman who is pregnant or is breastfeeding may not participate in this research. A pregnancy test will be performed for any woman who has neither been amenorrheic for the previous 12 months nor surgically sterilized and who is sexually active and not using an acceptable means of birth control (condom, diaphragm and spermicide, oral or injected contraceptives, IUD) and who wishes to participate in this study. It is the responsibility of the patient to use acceptable methods of birth control (condom, diaphragm and spermicide, oral or injected contraceptives, IUD, surgical sterilization, and abstinence). If the patient is a woman who can bear children and suspects pregnancy during the time she receives treatment in this study, she should notify the study staff immediately. If she is pregnant, her study medication will be discontinued.

The exclusion criteria are:

1. Women must not be pregnant, breast feeding, or plan to be pregnant during the course of the study.
2. The presence of ongoing bleeding.
3. The presence of a known bleeding disorder (e.g., hemophilia or von Willebrand's disease)
4. Recent bleeding episode requiring transfusion within 12 weeks of entry.
5. The presence of acute ulcer disease. Acute ulcer disease is defined as a new diagnosis of peptic disease including esophagitis, gastritis, or ulcer or the initiation of treatment for acute ulcer disease with proton pump inhibitors, H2 blockers or therapy for Helicobacter pylori within three months prior to obtaining consent.
6. Known allergy or adverse reaction to Aggrenox or any of its study components (dipyridamole and aspirin).
7. Required use of warfarin, dipyridamole, non-steroidal antiinflammatory drugs or other antiplatelet agents other than aspirin.

8. Current uncontrolled hypertension with systolic blood pressure in excess of 200 mm Hg or diastolic blood pressure in excess of 115 mm Hg.
9. Baseline platelet count less than 75,000/mm^3.
10. Known advanced liver disease with decompensated cirrhosis, jaundice, ascites or bleeding varices.
11. Current problem with substance abuse.
12. Concurrent participation in another medical intervention trial.
13. Anticipated non-compliance with medical care based on physician judgment.
14. Patient refusal.

3.3 Randomization

Subjects who have been enrolled in the study will be randomized within 2 days after successful placement of a new arteriovenous graft. Administration of the study drug should begin immediately following randomization. The optimal time for randomization and initiation of study medication would be in the postoperative recovery room after verification that a graft was placed. If the surgeon reports that the graft thrombosed in the operating room or in the recovery room, the patient should not be randomized. Subjects will be randomized to either Aggrenox or matched placebo in a ratio of 1:1. Randomization will be stratified by Clinical Center and by access (lower arm or at another site). A random permuted block design will be used to assure approximate balance over time. Randomization will be performed via the internet using a Web browser following verification of eligibility by the Data Coordinating Center. Stratification based on Clinical Center is designed to minimize the influence that differences in baseline risk between different centers might have on study outcome. While one source of variability is likely to be surgical expertise (62), the number of access procedures done by each surgeon is expected to be so small that stratification by surgeon is not likely to be feasible. The location of the graft in the upper or lower arm has been shown to strongly influence graft survival in some studies and thus randomization will also be stratified by this variable (55, 63, 64). Since leg grafts and other heroic graft sites (e.g., necklace graft) have a high flow rate, they will be categorized as an upper arm graft for the purpose of stratification (63).

Use of angiotensin converting enzyme inhibitors has recently been reported in two retrospective studies to have a strong effect to prevent access failure (119, 120). The results are preliminary, however, the use of ACE inhibitors in dialysis patients is increasing. If ACE inhibitors or ARBs do have a large effect on access survival then this could impact on the response to Aggrenox. Therefore, whether a patient was on an ACE inhibitor or ARB at baseline will be included as a pre-specified covariate in the primary analysis. The use of these agents will not be controlled and may change during the course of the study. The ongoing use of these agents will be recorded at the monthly visits and that data will be used to further analyze for a possible relationship between use of these agents and access failure. In addition, hypoalbuminemia has been reported to be a strong risk predictor of access failure (55, 63, 64). Therefore, serum albumin at baseline will be included as a second prespecified covariate in the primary analysis. Other potential prognostic factors such as diabetes and vascular disease have not been consistently shown to be strong predictors of access failure, and will not used as stratification factors or as covariates in the primary analysis.

3.4 Blinding

Treatment assignment will be masked to both patients and study personnel. Aggrenox and matching placebo will be provided by Boehringer-Ingelheim. Dipyridamole produces vasodilation that might lead to an increase in access blood flow detectable by flow monitoring. However, the difference in access flow rate between subjects will likely be larger than the effect of dipyridamole. Since the study involves new grafts, there will be no prior baseline access flow measurement for comparison and therefore it is unlikely that the blinding will be unmasked by flow monitoring. Initiation of dipyridamole will cause transient headache in some patients that could unmask the blinding in those patients. The aspirin component of Aggrenox might also unmask the study blind due to increased

difficulty with hemostasis at the end of dialysis. However, patients who receive Aggrenox or placebo at the time of receiving a new access will not have a baseline comparison to discern whether the study drug has altered hemostasis. Moreover, aspirin is commonly used in ESRD patients and this will tend to obscure any noticeable difference between the study patients on Aggrenox and the general hemodialysis population.

Aggrenox has a small dose of aspirin that could predispose to bleeding. We anticipate that unblinding may be required in the following two circumstances: 1) prior to the performance of emergency surgery, and 2) if there is life-threatening hemorrhage where the transfusion of platelets to reverse the antiplatelet effects of therapy is indicated. When it is absolutely necessary that a study medication code be released, the Data Coordinating Center will reveal the medication for a given patient to the study nephrologist at the facility. After unblinding, the patient should be continued in the trial on study medication if the subject did not have a major or life-threatening bleed and there are no other medical contraindications to doing so.

4. STUDY TREATMENT PLAN

4.1 Study Visits

Subjects should be seen prior to creation of the access for enrollment and collection of baseline data. The subject will be evaluated again within 2 days after creation of the new access to confirm that an eligible graft had been placed and is patent. If the access is patent, the subject will be randomized into the study and the first months supply of study medication will be provided. The patient will be asked to take their first dose of medication at that time.

Following randomization, subjects will be seen at monthly intervals throughout the duration of the study. It is anticipated that most subjects will be undergoing hemodialysis and will be seen at the time of a scheduled hemodialysis session. For subjects on hemodialysis, each monthly visit will include a measurement of access flow rate along with collection of study data including an assessment of access related procedures, complications, hospitalizations and compliance with the study medication (Section 6.2 below). For those subjects not yet on hemodialysis a monthly visit will need to be arranged to assess access patency and collect study data.

The subject will remain on study medication until the primary endpoint is reached, at which point the medication will be terminated. The monthly visit schedule will continue until the first regularly scheduled monthly visit following the primary endpoint. At closeout, the functional status of all accesses and survival of all patients that had been enrolled in the study will be determined and if total site failure or death has occurred, the time of these events will be recorded. Each monthly visit will include an assessment of potential adverse events.

4.2 Study Drug Administration

The first dose of study medication should be administered starting within 2 days of access creation. The Aggrenox or matched placebo should be taken as one pill twice a day. Assuming there are no reasons for early termination of the study medication, the study medication should be administered throughout the duration of the study until the primary endpoint occurs or study termination.

Each unit will need to establish a mechanism for storing the study medication and for dispensing the study drug to the subject within 2 days after surgery and then monthly thereafter. The study coordinator or the investigational pharmacy may handle storage and dispensing of the study medication as appropriate for each unit. The study medication will be mailed from a central pharmacy to the designated study coordinator or investigational pharmacy at each unit.

4.3 Intercurrent Events and Interruptions in Treatment

At the time of enrollment, patients will be provided with an information card containing a description of the study and study personnel contact information. The information card should facilitate rapid communication with study personnel if adverse events occur or treatment interruptions need to be considered.

4.3.1 Bleeding

Aggrenox has a small dose of aspirin that will increase the risk of bleeding. Bleeding will be classified as either minor, intermediate, major, life-threatening or fatal. Minor bleeding events are episodes of bleeding that did not require an event-related visit or follow-up or discontinuation of the study drug. Intermediate bleeding is a bleeding event that does not meet criteria for a major bleed but required an event-related visit with a health care provider or temporary discontinuation of study medication. Examples of minor or intermediate bleeds might include superficial cuts, abrasions, bruises, nose bleeds, or vaginal bleeding events. The presence of a hemoccult positive stool alone that leads to non-emergent evaluation such as a colonoscopy and is not associated with a 2 g/dl drop in hemoglobin or the need for a transfusion will be considered an intermediate bleeding event. Major bleeding is defined as a confirmed retroperitoneal, intra-articular, intraocular, or intracranial bleed or any bleed that leads to a drop in hemoglobin by 2 g/dl and requires hospitalization or the need for a transfusion. Life-threatening bleeding is any bleed that leads to a drop in hemoglobin of ≥5 g/dl, requires emergency surgical intervention, causes a symptomatic intracranial hemorrhage, or requires a transfusion of more than 4 units of packed RBCs or whole blood. Fatal bleeding is any bleed that causes or precipitates death.

Management of bleeding should be handled as for a patient on aspirin. For minor episodes of bleeding (e.g., superficial abrasion or nose bleed) conservative measures to control the bleeding should suffice without the requirement for discontinuing study medication. Short-term discontinuation of study medication during an intermediate bleeding episode with re-institution when stable is allowed. If the patient has a major or life-threatening bleed the study medication will be discontinued and not restarted. In the event of a cerebrovascular accident occurring during active treatment, computed tomography or magnetic resonance imaging should be performed to exclude intracerebral hemorrhage. For intermediate bleeds the decision to stop study drug will be made by the physician(s) caring for the patient. If the patient has a major or life-threatening bleed the study medication will be discontinued and not restarted unless the bleed is caused by either a surgical procedure or trauma and it is established 1) that the cause of bleeding has been eradicated, and 2) that the bleeding event does not reflect an underlying bleeding tendency or predispose to recurrent bleeding. Study drug resumption in this situation must be approved by the physician(s) caring for the patient. Bleeding events will be actively monitored and recorded by the study coordinator throughout the patient's participation on the study. An expert panel will review all major and life-threatening bleeds as well as a randomly selected subset of other bleeding events.

4.3.2 Surgery or Other Invasive Procedures

If the patient requires elective surgery or other invasive procedures with a risk of bleeding, the study medication should be stopped 7 days prior to the procedure and resumed the day after the procedure if there has not been inordinate bleeding and if the physician performing the procedure agrees. If the patient requires emergent surgery where the risk for bleeding is high (e.g., neurosurgery) the study medication should be stopped and consideration given to revealing the medication code and administering platelet transfusion if the patient has been receiving active drug.

4.3.3 Other Adverse Events

Aggrenox has been associated with a higher incidence of headaches and GI disturbances, particularly diarrhea compared to placebo. However, these tend to get better with continued use of the drug (48). If these events occur, efforts should be made to treat them conservatively (e.g., acetaminophen for headache or psyllium for diarrhea) and continue the study medication. If the symptoms persist then a trial of withdrawing the study medication for a week can be performed to see if the symptoms resolve. If the symptoms do resolve and the subject agrees, rechallenge with the study medication should be considered to confirm that it is the cause of the symptoms before stopping the study medication completely. A committee of study investigators will review the reasons leading to permanent withdrawal from therapy.

4.3.4 Concomitant Medications

The risk of bleeding is likely to be increased if Aggrenox is used in combination with anticoagulants or antiplatelet agents. In addition, the risk of GI complications including ulcers is likely to be increased by combined use of Aggrenox with nonsteroidal anti-inflammatory agents. Every effort should be made to avoid the use of anticoagulants (e.g., warfarin), antiplatelet agents (e.g., clopidogrel, ticlopidine or sulfinpyrazone) or nonsteroidal anti-inflammatory agents (e.g., ibuprofen) in patients while on study medication. If there is an absolute medical indication for any of these agents (e.g., anticoagulants for atrial fibrillation or deep venous thrombosis) then therapy with the study medication should be discontinued and the patient continued to be followed for the duration of the study. Likewise, if a medical requirement for Aggrenox or dipyridamole arises then the study medication will be stopped and the patient followed for the duration of the study. The use of aspirin for an accepted medical indication (e.g., unstable angina or secondary prevention of stroke or myocardial infarction) or the use of intermittent heparin for hemodialysis will not constitute a reason for stopping the study medication. Management of pain should be attempted first with acetaminophen, codeine or other analgesics.

4.3.5 Risk of Adenosine

The dipyridamole in Aggrenox can potentiate the action of adenosine used in some heart stress tests (e.g. adenosine-thallium nuclear medicine stress test). Adenosine is also occasionally used to block certain supraventricular arrhythmias. The study medication should be discontinued 2 days before using adenosine for cardiac function testing. The study medication can be restarted after the stress test is completed. Adenosine should be avoided or used cautiously in any study subject who develops a supraventricular tachyarrhythmia. Alternate methods of cardiac stress testing, such as dobutamine echocardiography are acceptable for subjects on the study medication.

4.3.6 Discontinuation of Therapy

Adverse events leading to cessation of study drug, but not termination from the study will include:

1. Development of an intestinal ulcer or gastrointestinal bleeding while on the study medication.
2. An adverse event attributed to the study medication such as intolerable persistent headache, diarrhea or dizziness without other etiology that does not respond to medical management.
3. A bleeding disorder (e.g., a major or life-threatening bleed) that contraindicates the continued use of Aggrenox.
4. A new medical requirement for long-term anticoagulation or antiplatelet therapy other than aspirin.
5. A new medical requirement for using Aggrenox or dipyridamole.

4.4 Events Leading to Withdrawal from the Study

A patient will be withdrawn from the study for the following reasons:

1. Death
2. Loss to follow-up due to permanent transfer to another renal replacement modality or to a non-participating dialysis unit.
3. Withdrawal of consent.

4.5 Study Completion

Study participation will end at: 1) the first monthly visit following the primary endpoint, 2) patient withdrawal due to one of the reasons listed in Section 4.4, or 3) the end of the study. Study medication will be withdrawn at the time of the primary endpoint, patient withdrawal, and the end of the study. Total failure of the access site is defined as the complete cessation of function of the study access that cannot be restored and results in the need to place a new access at a distinctly different site (either catheter or arteriovenous shunt) to continue dialysis.

Data collection after study participation has ended will consist of the following:
At completion of the study it will be determined whether the access that was randomized into the study is still functional or not. If total site failure has occurred, the date of that occurrence will be determined. Hospitalization and mortality data will be obtained using national databases while the study is on-going and for up to five years after the study has ended.

5. ACCESS FLOW MONITORING

5.1 Rationale

Longitudinal observational studies have shown that an active access surveillance program can decrease the rate of graft thrombosis and may increase overall access survival (3, 23, 65, 66). Based on these studies, the guidelines from the Dialysis Outcomes Quality Initiative (DOQI) recommended an organized approach to access surveillance with regular assessment and tracking of access function to detect and treat access stenosis (3). Several approaches are used for access surveillance (3, 67) and there is currently no uniform approach to monitoring access function across all the Clinical Centers. Since the efficacy to detect stenosis before thrombosis varies between the different techniques, this may lead to heterogeneity in the event rate between units. For instance, dialysis units that use flow monitoring to detect access dysfunction are likely to detect access stenosis and refer a patient for a corrective procedure (the endpoint) earlier than units who use alternate surveillance strategies. The type of primary endpoint would also be affected, as programs with flow monitoring will have more angioplasties rather than thrombosis as the primary endpoint (68). Of the currently available techniques, routine monthly measurement of access flow rate offers the most accurate and practical technique to detect access stenosis (68). To promote uniformity between Clinical Centers, routine monthly flow monitoring was therefore chosen as the standard access surveillance technique for the study.

One major advantage of flow monitoring is the ability to make a better assessment of the mechanism of action of the study drug. This is something unique to the hemodialysis access that cannot be easily done in studies of other vascular beds. For instance, initial access flow rate may be an important inverse predictor of access failure (28, 69, 70). As a vasodilator, dipyridamole may act to increase (or decrease, if it causes a “steal” syndrome) the initial access flow rate and this might help explain the observed outcome. In addition, if dipyridamole acts to inhibit the development of access

stenosis this will be discovered by comparing the rate of decline of access flow rate between placebo and dipyridamole. The resulting fistulogram will then confirm anatomically the hemodynamic evidence of stenosis obtained from the access flow measurements. Thus access flow monitoring enhances our ability to detect a drug that inhibits vascular access stenosis. A potential concern is that routine flow monitoring leading to angioplasty of stenotic lesions prior to thrombosis may mask a potentially beneficial anticoagulant effect of a study drug. Nevertheless, access stenosis is the predominant underlying etiology of access thrombosis and access flow monitoring should enhance our ability to more rapidly and specifically detect pharmacological agents that inhibit this process. In addition, the enhanced accuracy to detect stenosis as the cause of access failure should improve secondary analyses of covariates that predict access stenosis.

5.2 Procedure for Measurement of Access Flow

The technique for measuring access flow rate using the saline infusion ultrasound dilution technique is based on the Fick principle and has been detailed by Dr. Depner (see Manual of Operations). At each monthly visit the study coordinator will obtain one measurement of access recirculation while in the standard configuration for dialysis (i.e., blood is being withdrawn using the needle closest to the arterial anastomosis and returned in the needle that is farthest away from arterial anastomosis of the graft). Then the lines will be switched and two measurements of access blood flow obtained in this reverse configuration. If the two measurements differ by greater than 10%, then a third measurement will be obtained. These measurements must be within the first two hours after starting dialysis. All blood flow measurements will be reported to the DCC.

Changes in cardiac output and blood pressure will directly alter access blood flow (i.e., access flow increases with increased cardiac output and blood pressure) (117). Cardiac output and blood pressure are influenced by many external factors that may vary between dialysis sessions including medications, volume status, the rate of fluid removal on dialysis or a new cardiac event. This will introduce variability into the measurement of access flow. We can not easily measure cardiac output on a routine basis but blood pressure will be recorded at the time the access blood flow is measured. The blood pressure recorded at the time of access measurement will be used to normalize the measured access blood flow to a standardized mean arterial pressure of 90 mmHg using the equation

$$nQb = mQb + ((90 - MAP)*8.6)$$

where nQb is the normalized access blood flow, mQb is the measured access blood flow, MAP is the mean arterial pressure calculated as (DBP + ((SBP-DBP)/3)) and the factor 8.6 is derived from the published regression equation for access flow rate on mean arterial blood pressure (117). In addition, every effort will be made to obtain the access flow readings within the first hour after starting dialysis. The time of the access flow measurement as well as the dialysis start time will be recorded.

The mean value of all the normalized access flow measurements obtained at each visit will be calculated and used to determine if the patient meets criteria for access evaluation. Each month the change in normalized access flow will be calculated as the difference between the current month's mean normalized flow measurement and the average of the first two measurements. The first flow measurement will be obtained as soon as possible after starting to use the access but no more than two weeks after starting to use the access for dialysis. The second measurement will be obtained approximately two weeks later. This second measurement can be no sooner than 1 week nor more than 1 month after the first access measurement. Thereafter, access flow measurements will be obtained at least monthly preferably timed from the date of the first access flow measurement and continue until one month after the primary endpoint or until study termination. When a flow measurement is found to meet criteria for access evaluation (see below) it is recommended that the results be validated with repeat flow measurement at a different dialysis session before sending the patient for angiography. This second confirmatory measurement should be done as soon as possible preferably within 2 weeks after the first measurement that met criteria for access evaluation.

5.3 Access Management Based on Access Flow Data

Studies with access flow monitoring have demonstrated that for arm grafts, an access flow rate less than 600 ml/min or a drop in access flow rate of 25% when the access flow rate is less than 1,000 ml/min is predictive of hemodynamically significant access stenosis (28, 69, 70). Based on these parameters an algorithm for the monthly surveillance of access flow rates has been developed. The algorithm is shown in Figures 5.1 (Calculating Study Baseline) and 5.2 (Regular Monthly Measurements). The current visit's flow measurement will trigger consideration for an angiographic evaluation if: i) the nQb is <600 ml/min, or ii) the nQb is < 1000 ml/min and is at least 25% below the study baseline flow (see Fig. 5.1). If angiographic evaluation of the access reveals a stenosis of 50% or more then a corrective procedure, most likely angioplasty will be undertaken to reverse the stenosis. This represents the primary endpoint of the study.

If based on these flow criteria the patient is referred for an angiogram that fails to detect a significant access stenosis (i.e., less than 50% stenosis) then the subject will not have reached the primary endpoint. Failure to find an access stenosis when the flow rate has met the targets for access evaluation may be due to a drop in cardiac output (e.g., from volume depletion or a recent myocardial infarction), technical error in making the access flow measurement, or a false negative result with angiography (i.e., missing a stenosis that was actually present). If the flow measurement the next month still meets a target for access evaluation then a new baseline will be established based on an average of the three values prior to the procedure and the one after the procedure. A further drop in access flow rate of 25% below this new baseline or a drop below 600 ml/min (if not already at or below this level) will lead to another referral for angiography. Monthly flow monitoring will continue until one month after the primary endpoint (to determine whether the access procedure restores access flow) or until the study ends.

Figure 5.1

Flow Diagram for AVG Surveillance - Calculating First Baseline

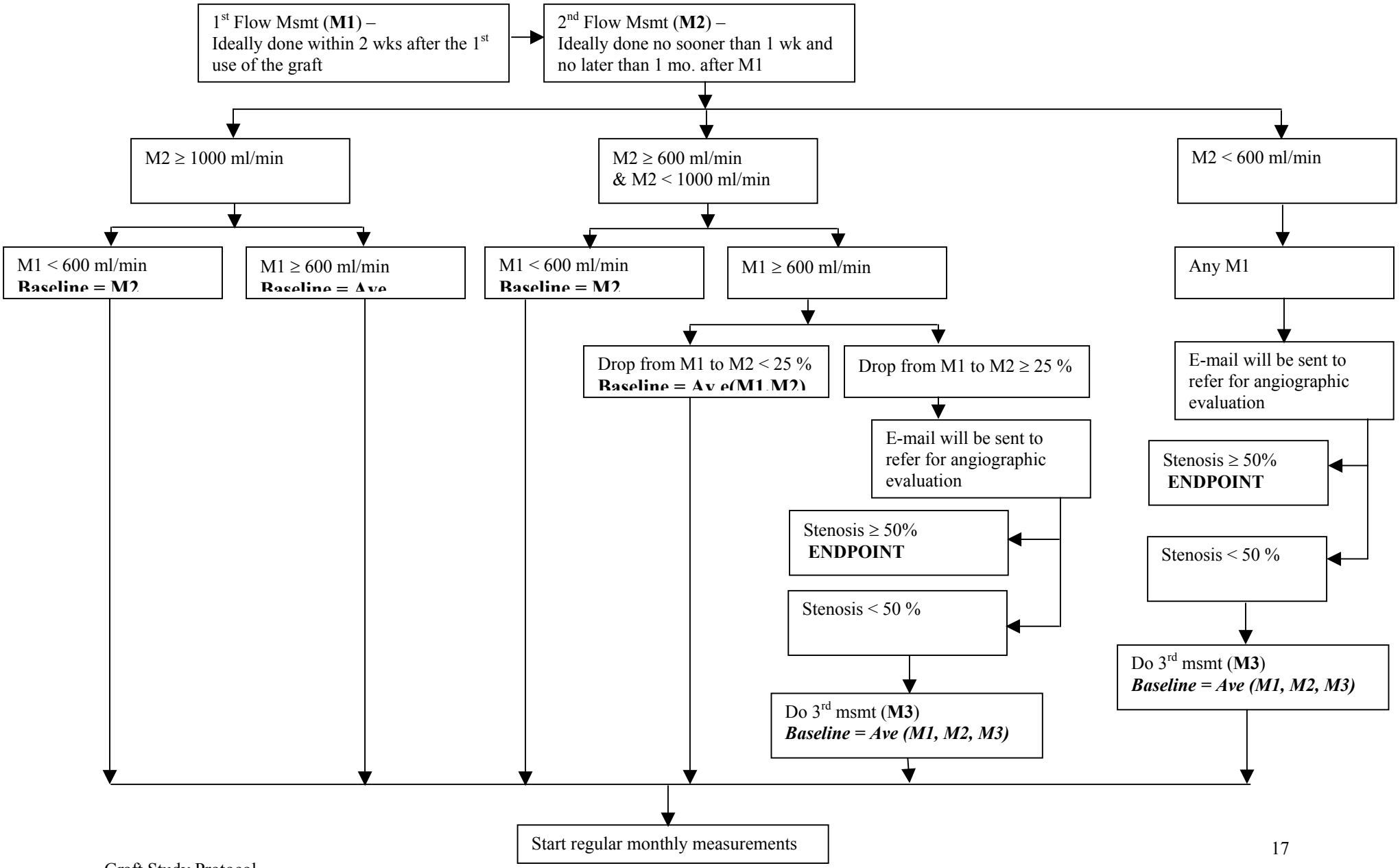
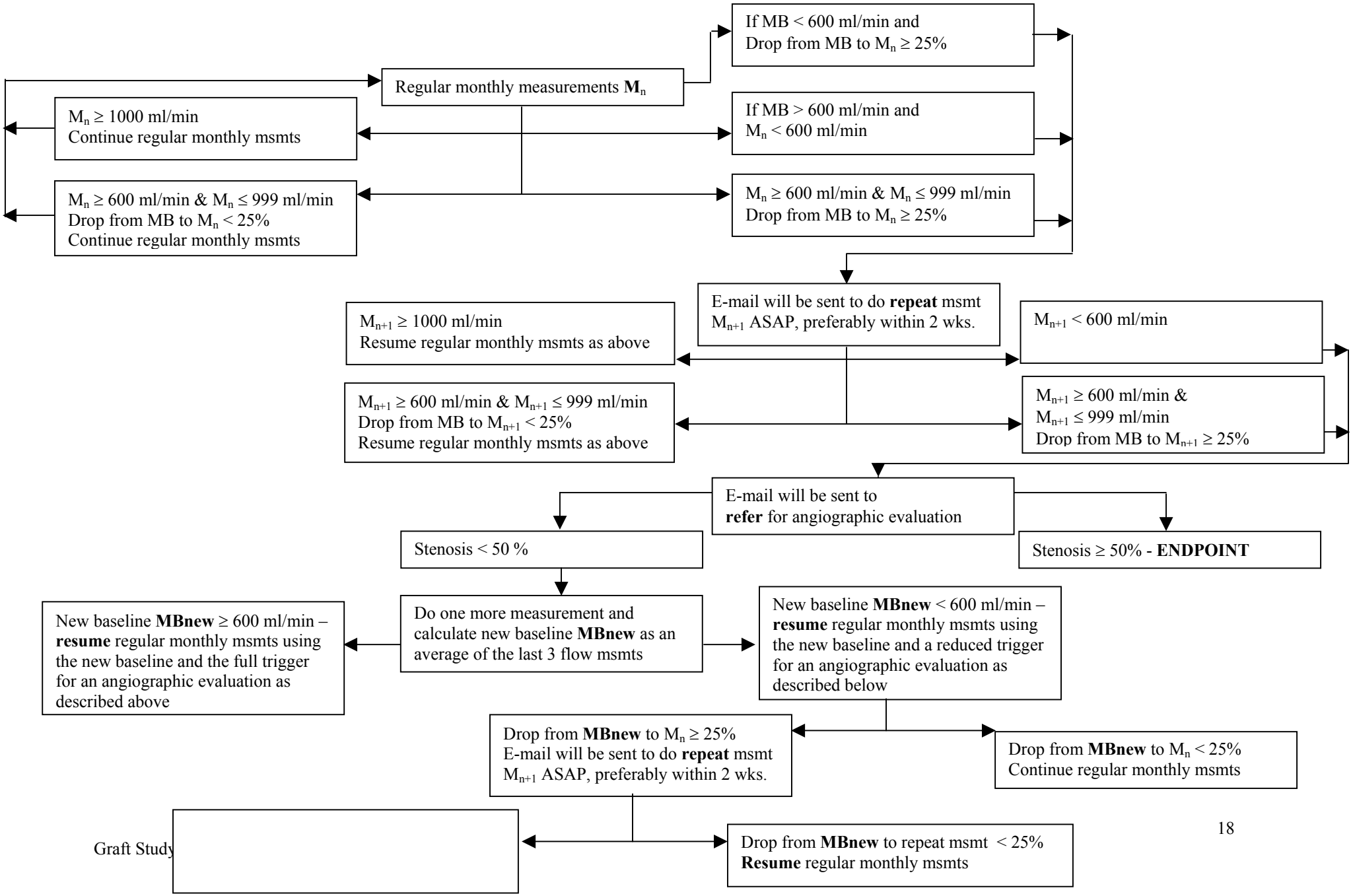


Figure 5.2

Flow Diagram for AVG Surveillance - Regular Monthly Measurements



5.4 Quality Control of Flow Monitoring

Quality control procedures for flow monitoring will include training flow monitoring technicians by manufacturer representatives and by ongoing review of the measurements (see Manual of Operations).

6. DATA COLLECTION

6.1 Baseline Data

The baseline evaluation is designed to: 1) ensure that subjects meet the inclusion/exclusion criteria, 2) obtain information regarding demographics, access history, medications, and medical history that may affect treatment response and risk of access failure, and 3) obtain information on medical history and laboratory tests to ensure that patients are not at risk for developing complications of therapy. Data should be collected as close to the time of graft creation as possible but no longer than 45 days prior, and should include:

1. Patient identification – demographic information (age, gender, race)
2. Patient's mailing address for study medication. If no suitable home address, medication will be mailed to the dialysis unit to provide to the patient
3. Date of enrollment
4. Date of ESRD; start date for hemodialysis
5. Cause of ESRD (diabetes, hypertension, polycystic kidney disease, glomerulonephritis, interstitial nephritis, hereditary nephritis, other)
6. Access history
   a. Prior arteriovenous access attempts – number, type, location, date(s) placed
   b. Prior central catheter placements (subclavian or int. jugular) – yes/no; right, left or both
   c. Current central catheter – type, site, date placed
7. Diagnoses (history of diabetes (duration, nephropathy, retinopathy, neuropathy), hypertension (duration), vascular disease (myocardial infarction, CABG, CHF, angina, stroke, TIAs, peripheral vascular disease, amputations), coagulopathy, or hyperlipidemia
8. List of current medications
9. Tobacco use (how much, age at start, currently smoking (yes/no), if not, when habit stopped
10. Quality of life questionnaire
11. Blood pressure & pulse – predialysis, sitting position
12. Height and weight
13. Periodontal disease (no obvious cavities or gingivitis, cavities or gingivitis, or edentulous)
14. Examine arms to note scars and evaluate number and location of any current functional accesses and previously failed access sites
15. Look for presence of current central catheter – Note type and location.
16. Baseline biochemical measurements - most recent within the last 45 days, record date CBC (hemoglobin, platelet count), and albumin.

6.2 Monthly Visits

The purpose of monthly visits is to: 1) assess access function and monitor for the development of access stenosis using flow monitoring, 2) obtain information on all access-related events and procedures relevant to the primary and secondary outcomes, 3) determine whether there have been changes in the medical condition or medications that might influence access survival or require discontinuation of the study medication, 4) report any adverse complications of the study medication

5) assess and encourage compliance with the study medication and follow-up. All the data elements listed in Section 6.2.2 below will be collected at each monthly visit up to the primary endpoint. Additional data elements will be collected at the first visit and at each third visit as listed below.

6.2.1 First Monthly Visit

At the first visit after creation of the access data on the type of graft material used and the location and configuration of the graft will be collected. In addition, the date of surgery and the surgeon will be confirmed. The date of first cannulation of the access for dialysis will be recorded as soon as it is available.

6.2.2 All Monthly Visits

1. Access recirculation and access blood flow within first 2 hours of dialysis (see Manual of Operations)
2. Blood pressure (sitting) predialysis (from chart) and at time of access blood flow
3. Person doing needle insertion (patient or nurse).
4. Problems with needle insertion in the last month (hematomas, multiple needle sticks, failed insertions)
5. Access related events (see list in Section 12.1)
6. Access related procedures (see list in Section 12.2) – indication, date of procedure, outcome
7. Hospitalizations – primary and secondary diagnosis, dates of admission and discharge
8. Compliance with study medications as assessed by patient interview and monthly pill count. Subjects will be asked to return pill bottles of study medication each month.
9. Current medications.
10. Monthly dialysis lab tests – serum albumin, hemoglobin, hematocrit, pre and post BUN, calcium, phosphorus. PTH when available every third month.
11. For incident patients not yet on dialysis the patency of the access will be determined by the presence of an audible bruit or a palpable thrill in the graft.
12. Adverse event monitoring (see Section 6.2.3 below)

6.2.3 Monthly Adverse Event Monitoring

Adverse events will be recorded at the monthly visits. Subjects will be asked the following questions:

1. Have you had any problems with your study medication? Describe them.
2. Have you had any hospitalizations? When and what was the reason?
3. Have you had any other new significant health problems? Describe them.
4. Have you had any episodes of significant bleeding?
5. Are you having any gastrointestinal symptoms such as heartburn or abdominal pain?

The responses to all these questions will be recorded and an assessment will be made as to whether the event is related to the study medication. For any hospitalizations or emergency room visits the medical record will be reviewed to determine the cause of the visit and whether it was likely related to the study medication. Particular attention will be given to whether a bleeding event precipitated the visit or hospitalization. For patients that might be questionable historians, the dialysis nurse caring for the patient will be asked whether they are aware of any adverse events, hospitalizations, or transfusions that have occurred in the preceding month. In addition, the patient dialysis logs will be examined to determine if the patient missed any sessions and the patient will be asked the reason for the absence. Serious adverse events are those that result in any of the following outcomes: death, a life-threatening adverse experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly or birth defect. All serious adverse events will be reported to the DCC within 24 hours of study personnel learning of the event.

6.2.4 Every Third Month

Response to quality of life questions will be obtained (71, 72).

6.2.5 Blood and DNA Collection

Blood and DNA samples will be collected for use in future research studies to assess risk factors for access failure and response to therapy. A sample will be collected once for each patient, preferably at the baseline visit. For those patients where this is not possible, collect the blood at the next possible visit.

6.2.6 Quality Control of Clinical Center Data

Each clinical study site will be visited once during year one and every other year for the remainder of the study. The site visit will consider recruitment, retention, patient compliance, adverse event monitoring and clinical center adherence to study procedures. During the data audit portion of the site visit, site visitors will examine a random subset of site clinical data for which source documentation would normally be available, such as date of birth and local laboratory data. Data on source documents at the clinical center will be compared with data in the DAC Study Database.

Bleeding is the major expected risk of therapy with Aggrenox. For purposes of safety and adverse event analyses, categorization of bleeding events will be made based on information transmitted from the clinical centers on the data forms with additional information obtained from source documents as needed. To assure that bleeding events that result in death are properly documented there will be central review of data on any subject who has had a bleeding event recorded in the study database within 30 days prior to death. The study's Data Coordinating Center will notify investigators about any subject who meets these criteria. The center will then send primary data including any emergency room or hospital discharge summaries relevant to the bleed as well as documentation relating to the subsequent death. This information will be reviewed by two independent physician study investigators to determine whether the cause of death was related to the prior bleed.

6.2.7 Study Closeout

At completion of the study it will be determined whether the access that was randomized into the study is still functional or not. If total site failure has occurred the date of that occurrence will be determined. Hospitalization and mortality data will be obtained using national databases while the study is on-going and for up to five years after the study has ended.

7. PRIMARY OUTCOME MEASURE

The primary outcome will be primary unassisted patency defined as the time from randomization until the first occurrence of either of the following:

1. Thrombosis
2. An access procedure performed or recommended to restore patency including angioplasty, thrombolysis, thrombectomy, or any surgical modification of the graft.

It is stipulated that access surgery done to modify the access because of a steal syndrome or congestive heart failure occurring within the first 30 days after creation of the access will not be considered an event for the primary composite outcome. However, loss of access function for any

reason will be considered a primary outcome. The primary endpoint will also be considered to occur if the subject is found to have a ≥50% access stenosis by angiography for which an intervention is recommended but refused.

For patients who are undergoing regular hemodialysis, failure to use the new graft by 12 weeks after access creation will be considered access site failure and the study will be terminated. For incident patients not yet on hemodialysis or prevalent patients whose new graft is not being used, patency of the access will be determined by monthly assessment of the graft for the presence of an audible bruit or a palpable thrill. Loss of both of these findings at any time in a patient whose access is not being used will be considered to be the primary event and the date of the endpoint will be the date of ascertainment by the study coordinator.

The primary endpoint will not include diagnostic studies (e.g., angiogram or ultrasound) that reveal a stenosis <50%.

8. SECONDARY OUTCOME MEASURES

8.1 Cumulative Patency: Time to Complete Access Site Failure

Complete loss of a functional access site is an outcome of major clinical importance. It is not economically feasible to continue the study drug and intensive monthly data collection for the duration needed for an adequately powered study of site failure. However, it is important to track this outcome at the closeout of the study to see if the trend is consistent with the effect seen for the study drug in the main trial. For this analysis, cumulative patency is the time from randomization to complete loss of the access site for dialysis regardless of the number of interventions required to restore or maintain patency. Loss of the access site is defined by the need to place a new access using new arteriotomy and venotomy incisions or by the abandonment of the prior access as defined by the need for a central venous dialysis catheter for a period of ≥ 1 month. Operationally the need for a new arteriotomy and venotomy sites will be detected by the need for a completely new site for the placement of the access. (Note that in most instances a chart review should not be needed to determine this endpoint). Procedures used to prolong the function of the access at the current site such as resection and replacement of part of the graft or changing just the site of the venous anastomosis will not be considered site failure). It is anticipated that a pharmacological agent that prolongs primary unassisted patency will also prolong cumulative patency even if the drug is stopped at the primary endpoint. The median cumulative patency in a control population without active flow monitoring and angioplasty is expected to be about 2 years [Hofstra, 1996 #60; Mattsson, 1997 #280; Kohler, 1999 #281]. An active access surveillance program will prolong access survival in the control population beyond 2 years but the exact duration is not well defined in the literature [Sands, 1995 #63; Safa, 1996 #101; Besarab, 1995 #62].

8.2 Patient Survival

It is important that the study drug not produce any adverse consequences that might be worse than the measured outcome. Aspirin contained in Aggrenox is expected to cause an increase in minor and major bleeding events but is not expected to increase serious or fatal bleeding events. On the other hand, aspirin is known to decrease the rate of arterial thrombotic events in high risk populations. Given the high rate of cardiovascular death in the hemodialysis population, aspirin might actually improve overall patient survival. Due to the importance of this issue, time from randomization to death has been designated as a secondary outcome variable. However, it is recognized that the power of the study to detect a treatment effect on mortality is limited.

9. STATISTICAL DESIGN

9.1 Sample Size Calculations

The rationale for each of the assumptions used to calculate the required sample size for the study is outlined below. All of the calculations are based on the primary outcome of primary unassisted patency. The power calculations assume a constant hazard rate for the primary outcome, with a one-year probability of access failure in the control group of 0.54. The calculations further assume an annual loss to follow-up of 22%, an annual dropout rate of 15%, and an annual dropin rate of 1%. Under the suggested predefined stopping rule (see below), a total of 1056 subjects will be required to have a 85% power to detect a 25% reduction in the rate of the primary outcome for Aggrenox compared to placebo. Under the assumption of a constant hazard rate, this corresponds to a 33% increase in median primary unassisted patency from 10.70 to 14.28 months. Assuming that there will be a total of 7 Clinical Centers with a total of 1136 new grafts placed per year, an enrollment rate of 31.0% would allow patient accrual to be completed by 3 years and the total study duration would not exceed 4 years. With the recommended stopping rule the expected study duration will be slightly under 3 years under both the null hypothesis of no treatment effect and the research hypothesis of a 25% benefit of Aggrenox.

Addendum: As of June 1, 2004 the study was extended to 48 months of recruitment with a minimum of 6 months of additional follow-up on the recommendation of the Data Safety and Monitoring Board (External Advisory Committee).

9.1.1 Event Rate

Primary unassisted patency rates for upper extremity grafts vary with patient selection, surgical expertise as well as site and configuration of the graft (55, 56, 63, 64). Recent studies that mirror the circumstances of this study reveal one-year primary unassisted patency rates of between 23% - 49% (6, 55, 56, 81). Due to limits in ascertaining early access failures, data from the USRDS likely underestimates overall access failure rates (6). The remaining studies report one-year primary unassisted patency rates of between 23% - 43% (55, 56, 81). Since study patients will likely do somewhat better than average a one-year primary unassisted patency rate of 46% was determined for the primary power calculations (i.e., a one-year probability of access failure of 0.54).

9.1.2 Effect Size

The study by Sreedhara found a 50% effect size for dipyridamole alone and 27% for dipyridamole plus aspirin to decrease thrombosis in new grafts (34). No other controlled trial of dipyridamole to prevent hemodialysis access failure has been reported. However, long-term follow-up of vein grafts used for coronary artery bypass have also found an effect size of 41% for aspirin plus dipyridamole to decrease the percent of veins that have a stenosis compared to placebo (45). Tempering these data is one retrospective report suggesting no effect of dipyridamole to prevent hemodialysis graft failure (33, 44). Looking at the effect of dipyridamole in the secondary prevention of occlusive arterial vascular disease (i.e., myocardial infarction and stroke), most studies have used a combination of aspirin and dipyridamole (82). The effect size in these studies was between 18% - 36% (82). However, in most studies the addition of dipyridamole was not shown to improve the outcome over aspirin alone (76). In contrast, in a large randomized, placebo-controlled double-blind study for secondary prevention of ischemic stroke involving 6602 patients, dipyridamole (200 mg bid; n=1654) was found to decrease the risk of stroke by 16% and the combination of aspirin plus dipyridamole (n=1650) reduced risk by 37% (47). In this study, low dose aspirin (25 mg bid) alone reduced the risk by 18% which is somewhat less than studies using a higher dose of aspirin (83). Nevertheless, this

large study demonstrates that dipyridamole alone is effective for secondary stroke prevention and the combination medication Aggrenox is better. Finally, with regard to restenosis after a vascular procedure, the data published to date would suggest no benefit of using lower doses of immediate release dipyridamole (57, 58, 74, 78). However, as discussed above these studies may not be relevant to angioplasty of venous lesions and the time-averaged concentration of dipyridamole would be much lower than that provided by Aggrenox. We are not aware of any clinical trials of Aggrenox after angioplasty in humans. However, dipyridamole has been effective in experimental models to prevent restenosis after angioplasty. Based on these studies and clinical estimates of what effect size would constitute a meaningful result, an effect size of 25% has been hypothesized for the primary outcome.

9.1.3 Subject Loss or Modality Transfer

Based on the data from the HEMO Study we anticipate that the rate of patient death, transfer to another treatment modality or loss to follow-up will be 22%.

Dropin and Dropout

Based on prior experience in large scale clinical trials, the annual rate of dropouts (patients randomized to the Aggrenox arm who stop taking active drug) was assumed to be 15%. The annual rate of dropins (patients randomized to the placebo arm who receive Aggrenox or a related drug) was assumed to be 1%.

9.1.5 Statistical Stopping Rule

The Steering Committee has recommended that the External Advisory Committee adopt an information-based stopping rule based on a boundary in which the study will be terminated early if therapy with Aggrenox is proven to be effective or the null hypothesis cannot be disproved under the current study design. Boundaries form the Wang-Tsiatis class (84) with shape parameters of 0 (corresponding to the O'Brien-Fleming stopping rule) are suggested for the boundary both for early rejection of the null hypothesis and early termination due to futility. A total of 6 looks equally spaced in information time are planned.

9.2 Data Analysis

9.2.1 Interim Monitoring and Analysis

An independent External Advisory Committee will monitor the safety of the patients during the course of the study and to perform the interim efficacy analysis.

9.2.2 Final Analysis

9.2.2.1 Baseline analyses

To assess external generalizability, the demographic, clinical, and dialysis treatment characteristics of patients who are randomized will be summarized to characterize the study population and then contrasted with the characteristics of patients who are screened but not randomized. The randomized patients will also be compared to the general population of hemodialysis patients characterized in the USRDS. The specific eligibility and exclusionary criteria by which patients are excluded from randomization will be tabulated. Demographic and clinical characteristics will be compared among the Clinical Centers and between the treatment groups to identify any imbalances.

9.2.2.2 Primary Analysis

The primary statistical analysis will compare the effects of the Aggrenox and placebo interventions on primary unassisted patency as in Section 7. This analysis will be conducted using a Cox proportional hazards regression analysis (85) with stratification by Clinical Center and graft location (lower arm vs. another site). ACE inhibitor or ARB usage at baseline and serum albumin at baseline will be included as pre-specified covariates. The comparison of the Aggrenox and placebo interventions in the primary analysis will be carried out using an intent-to-treat strategy in which patients are retained in their randomized groups regardless of their compliance to the treatments. A 2-sided hypothesis test will be conducted at the 5% level of significance.

In accordance with the intent-to-treat format, events defining the primary unassisted patency outcome which occur after medication stop points will be counted as events in the primary analysis. However, the primary Cox regression analysis will be censored at the following events: death, renal transplant, switch to peritoneal dialysis or home dialysis, or transfer to a center not participating in the trial. Censoring these events is consistent with previous studies of access survival (34, 56, 86-88), and is necessary because the alternative strategy of incorporating them in the primary outcome would unacceptably reduce the hypothesized treatment effect. However, because they occur frequently in dialysis patients, it is recognized that censoring these events exposes the primary treatment comparison to the possibility of bias due to informative censoring (89).

The cumulative incidence of events for the primary outcome will be summarized graphically by Kaplan-Meier survival curves in which death, transplant, modality switches, and transfers are censored. The Kaplan-Meier curves will estimate the distribution of unassisted patency assuming independent censoring in a hypothetical population where the censoring events are assumed not to occur. In addition to the standard Kaplan-Meier curves, we will summarize the marginal cumulative incidence of the composite outcome while treating death, transplant, and modality switches as competing risks (90, 91). In this approach, the cumulative incidence curves estimate the marginal cumulative probabilities of occurrence of the composite event while acknowledging the absence of the composite event following death, transplant or modality switches.

9.2.2.3 Explanatory Analyses of the Primary Outcome

Explanatory analyses will be conducted to more fully characterize the relationship between the primary outcome, randomized group, and prognostic covariates based on interactive analysis of the data. Variable subset selection will be used to develop multivariable Cox regression models relating the hazard rate for access procedures to the randomized treatment groups and prognostic demographic factors, baseline biochemistry measurements, and other baseline variables. Nonparametric regression methods will be used to investigate possible nonlinear relationships between the hazard rate and prognostic factors (92, 93). Models with time-dependent covariates will be used to assess the association of the risk of access procedures with follow-up covariates (94), and interactions between Aggrenox and other factors will be investigated (95). The possibility of nonproportional hazards will be investigated by log-log plots (96) and by modeling the interaction of follow-up time with the Aggrenox - placebo comparison.

Sensitivity analyses to evaluate the possible influence of informative censoring in the primary Cox regression analysis will be conducted by taking advantage of the observations that several of the factors which have been found to be prognostic of the duration of graft patency are also related to the censoring variables. These include low serum albumin, greater age, diabetes, and a history of cardiovascular disease. Accordingly, the Cox-regression coefficients from the primary analysis will be compared to the coefficients from expanded Cox regression models which includes all baseline factors which are found to be associated with both the primary outcome and with at least one of the censoring variables. Second, recently proposed methods for survival curve estimation incorporating data from longitudinal prognostic covariates (97, 98, 99) will be used to estimate the time-to-occurrence of the primary composite outcome within the two treatment groups while accounting for follow-up blood

flow measurements prior to censoring. These methods would reduce the bias due to informative censoring due to any process in which the censoring is associated with the access blood flow measurements.

9.2.2.4 Secondary Outcomes

Time from randomization to the secondary outcome of site failure will be analyzed using a Cox regression model similar to that used in the primary analysis, with the same stratification factors, adjustment for baseline serum albumin and the same censoring variables. Time from randomization to death, and time from randomization to the composite of death or site failure will also be analyzed by Cox regressions with the same stratification factors and adjustment for baseline albumin as in the primary analysis. As for the primary analysis, censoring events include renal transplant, switch to peritoneal dialysis or home dialysis, or transfer to a center not participating in the trial. Cox models with cause-specific hazard rates will be used to analyze the specific cause of the primary events (e.g., events may be classified as being triggered by stenosis or clotting).

The effect of Aggrenox on the change in access blood flow over time (considered as a continuous variable) will be examined by longitudinal mixed effects models (100) or generalized estimating equations (101, 102). Joint models incorporating the longitudinal changes in access blood flow and the time-to-first access procedure will also be considered (103).

9.3 Data Quality Control

As previously noted, Clinical Center data will be checked by auditors during site visits. Additional quality control checks on each Clinical Center will include 1) time from form completion to data entry, 2) time to response to data discrepancy inquiries, and 3) rates of missing forms and procedures, for example.

The quality of the DCC's work will be checked by looking at how often the study database is down, how often an ineligible patient is randomized, and number of days from the time a Clinical Center responds to a data discrepancy inquiry to the time the DCC makes a database correction, for example.

10. TREATMENT EFFECTS AND SAFETY MONITORING

An External Advisory Committee (EAC), composed of independent experts in the fields of nephrology, biostatistics, and clinical trials, will review the accumulating data with regard to safety and efficacy. The members of the EAC are not involved in the conduct of the trial and have no affiliation with the drug manufacturers. Summary reports of the EAC will be submitted to all IRBs involved in the trial.

The EAC may terminate the trial early if one of the interventions (Aggrenox or placebo) is shown to be superior at an interim analysis based on the statistical stopping guideline (Section 9.1.5). The EAC will also consider comparisons of potential adverse events between the treatment arms. Conditional power calculations and estimates of the recruitment rate will also be provided at interim analyses so that the EAC can assess whether the trial should be terminated early in the event of unexpectedly low recruitment or trends in the treatment group comparison indicating futility of continuation of the study.

Serious adverse events are those that result in any of the following outcomes: death, a life-threatening adverse experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly or birth defect. All serious adverse events will be reported to the DCC within 24 hours of study personnel learning of the event. Information not available at the time of the initial report will be submitted to the DCC as a follow-up report. The DCC will be responsible for distributing safety reports to the Clinical Centers, the EAC,

and NIDDK. NIDDK will submit safety information to the FDA. Summary reports of adverse events will be submitted to all IRBs monitoring the trial. Additional reporting to IRBs will be performed according to local IRB policy. Non-serious adverse events will be reported to the DCC using the appropriate data forms.

11. REGULATORY CONSIDERATIONS

11.1 Institutional Review Boards (IRBs)

The protocol will be submitted to the IRB of each Clinical Center for review and approval. Clinical Centers may not recruit patients into the trial until approval of the protocol by their IRB. Protocol amendments and changes will be submitted to the IRB and approval must be received before implementation. All patients enrolled in the trial must sign and date an IRB-approved consent form and medical records release form before any study related procedures are undertaken. Study personnel will explain the study and answer all of the patient's questions before asking the patient to sign and date the consent form.

11.2 Confidentiality of Patient Data

All patient data will be maintained in a secure location. Data collected from study evaluations will be identified by study identification codes. Identifying features including names and addresses will be provided to the DCC, but kept in a secure file separate from the study database. Social Security numbers will be provided to the DCC only with additional written consent from the patient, if required by the local IRB. If such consent is obtained, the Social Security number will be kept in a secure file separate from the study database and will be used to obtain patient-specific hospitalization, medical procedures, and death data from databases other than those maintained for this trial. Patients can withdraw consent for continued access to such databases at any time. Clinically relevant information obtained as a result of participation in this trial may be placed in the patient's medical record as progress notes.

12. ACCESS RELATED EVENTS AND PROCEDURES

12.1 List of Access Events that Might Lead to Access Evaluation

1. Meets flow surveillance criteria for possible stenosis (see flow surveillance algorithm)
2. Thrombosis (loss of palpable access flow)
3. High venous pressures
4. Inability to achieve desired blood flow rate
5. Excessive bleeding post needle removal
6. Lower than desired kT/V
7. Inability to cannulate access
8. Access pain
9. Infection
10. Aneursym
11. Pseudo-aneursym
12. Arm swelling

13. Ischemia of distal extremity
14. High output state
15. Access hemorrhage
16. Neurological changes in access arm
17. Other

12.2 List of Access Related Procedures

1. Imaging – no intervention
   a. Fistulogram
   b. Doppler ultrasound
   c. Other (e.g., MRI)
2. Interventions
   a. Angioplasty – done either by interventional radiology or surgery
   b. Stent
   c. Thrombolysis
   d. Thrombectomy
   e. Surgical debridement
   f. Surgical revision (partial or complete resection of graft material; bypass of prior graft site using new arterial or venous anastomosis)
   g. Surgical creation of new access site
   h. Other (rotational myotomy, etc.)

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