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Design of the Dialysis Access Consortium (DAC) Aggrenox prevention of access stenosis trial

*Bradley S Dixon[a], Gerald J Beck[b], Laura M Dember[c], Thomas A Depner[d], Jennifer J Gassman[b], Tom Greene[b], Jonathan Himmelfarb[e], Lawrence G Hunsicker[a], James S Kaufman[c], Jeffrey H Lawson[f], Catherine M Meyers[g], John P Middleton[f], Milena Radeva[b], Steve J Schwab[f], James F Whiting[e] and Harold I Feldman[h] for the DAC Study Group**

Background Surgically created arteriovenous (AV) grafts are the most common type of hemodialysis vascular access in the United States, but fail frequently due to the development of venous stenosis. The Dialysis Access Consortium (DAC) Aggrenox Prevention of Access Stenosis Trial tests the hypothesis that Aggrenox (containing dipyridamole and aspirin) can prevent stenosis and prolong survival of arteriovenous grafts.

Methods This is a multicenter, randomized, double-blind, placebo-controlled trial that will enroll 1056 subjects over four years with one-half year follow-up. Subjects undergoing placement of a new AV graft for hemodialysis are randomized to treatment with Aggrenox or placebo immediately following access surgery. The primary outcome is primary unassisted patency defined as the time from access placement until thrombosis or an access procedure carried out to maintain or restore patency. The major secondary outcome is cumulative access patency. Monthly access flow monitoring is incorporated in the study design to enhance detection of a hemodynamically significant access stenosis before it leads to thrombosis.

Results This paper describes the key issues in trial design, broadly including: 1) ethical issues surrounding the study of a clinical procedure that, although common, is no longer the clinical intervention of choice; 2) acceptable risk (bleeding) from the primary intervention; 3) inclusion of subjects already receiving a portion of the study intervention; 4) inclusion of subjects with incident rather than prevalent qualifying clinical conditions; 5) timing of the study intervention to balance safety and efficacy concerns; and 6) the selection of primary and secondary study endpoints.

Conclusions This is the first, large, multicenter trial evaluating a pharmacologic approach to prevent AV graft stenosis and failure, an important and costly problem in this patient population. Numerous design issues were addressed in implementing the trial and these will form a roadmap for future trials in this area. *Clinical Trials* 2005; **2**: 400–412. www.SCTjournal.com

Introduction

The number of patients on hemodialysis in the United States has doubled over the last eight years, and continues to grow [1]. In order to accomplish hemodialysis, the patient must have a suitable vascular access to allow connection to the hemodialysis machine. There are three types of vascular

[a]Veterans Affairs Medical Center and University of Iowa School of Medicine, Iowa City, IA, USA, [b]Cleveland Clinic Foundation, Cleveland, OH, USA, [c]Boston University School of Medicine, Boston, MA, USA, [d]University of California School of Medicine, Davis, Sacramento, CA, USA, [e]Maine Medical Center, Portland, Maine, USA, [f]Duke University Medical Center, Durham, NC, USA, [g]National Institute of Diabetes and Digestive and Kidney Disease, Bethesda, MD, and [h]University of Pennsylvania School of Medicine, Philadelphia, PA, USA
*See Appendix 1.
Author for correspondence: Bradley S Dixon, Nephrology Division, University of Iowa School of Medicine, E300D GH, 200 Hawkins Drive, Iowa City, IA 52242–1081, USA. E-mail: bradley-dixon@uiowa.edu

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access: 1) an autogenous fistula constructed by directly connecting the patient's artery and vein, typically at the wrist or above the elbow; 2) a graft constructed by interposing a segment of tubing (typically polytetrafluoroethylene) between an artery and vein, usually in the arm; or 3) a catheter permanently inserted in a vein in the neck or chest. Although an autogenous fistula is the recommended vascular access, an AV graft has been the predominant type of access used in the USA. One-year primary unassisted patency for an AV graft ranges from 23 to 43% [2–5]. Although an AV graft can often be salvaged after thrombosis, the secondary patency for an AV graft, defined as the time from access creation to total loss of the access site, is only 59–65% at one year [2–5]. The expense of creating and maintaining vascular access in this patient population is therefore high, and accounts for a significant portion of expenditures in the dialysis population [6–8]. Costs for access-related problems have been recently estimated to be between 8 and 11% of total Medicare ESRD spending, or between $0.7 and 1 billion per year [7]. Vascular access is clearly a problem of major importance for both the hemodialysis patient population and the US health care system.

The primary mechanism for graft failure is neointimal hyperplasia leading to stenosis and access thrombosis [9,10]. Histochemically, the neointimal thickening consists predominantly of vascular smooth muscle cells and associated extracellular matrix material [11–14]. Increased cellular proliferation of smooth muscle cells and endothelial cells is a well-established characteristic of the lesion and is present within the neointima, media and adventitia [12–14]. These observations suggest that agents that inhibit smooth muscle proliferation or angiogenesis may be useful to prevent neointimal hyperplasia and graft failure.

Two randomized controlled trials, one that examined the anticoagulant warfarin, and the other that examined the combination of antiplatelet agents clopidogrel and aspirin, found no significant effect to prolong access graft survival [15,16]. These studies suggest that antithrombotic therapy alone may not be effective without also inhibiting the neointimal hyperplasia leading to access stenosis. In two small, randomized controlled studies, dipyridamole and fish oil have been reported to prolong graft survival [17,18]. Dipyridamole was chosen for our trial because it had been reported to prevent graft thrombosis and there was experimental evidence that it could inhibit neointimal hyperplasia.

Dipyridamole, a pyrimidopyrimidine compound, is a coronary vasodilator that was first introduced for the treatment of coronary ischemia [19]. Subsequently, it was found to have antiplatelet effects and has been used, typically in conjunction with aspirin, to prevent arterial thrombosis [19,20]. Dipyridamole inhibits adenosine uptake and has been shown to inhibit vascular smooth muscle cell proliferation *in vitro* via adenosine A2B receptors [21,22] and to inhibit neointimal hyperplasia after balloon injury to the carotid artery in rabbits [23,24]. In clinical studies, dipyridamole in combination with aspirin has been shown to decrease the incidence of late stenosis in coronary bypass vein grafts [25,26]. Extended-release dipyridamole has also been shown to be effective as a single agent in the secondary prevention of stroke [20].

The effect of dipyridamole and aspirin on arteriovenous graft thrombosis was examined in a randomized placebo-controlled trial [17]. In this small study, immediate-release dipyridamole, but not aspirin, was effective in preventing access thrombosis in newly created grafts. 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 [17]. Subsequent *in vitro* studies demonstrated that dipyridamole, but not aspirin, inhibited proliferation of vascular smooth muscle cells *in vitro* [27,28]. Hence, dipyridamole may act to reduce arteriovenous graft (AVG) thrombosis by inhibiting neointimal proliferation rather than as an antithrombotic agent.

Immediate-release dipyridamole must be taken three times a day and has variable absorption that depends on an acid environment in the stomach [29,30]. To address this concern, Aggrenox (Boehringer–Ingelheim), which contains a combination of extended-release dipyridamole and aspirin, was chosen for the study. Aggrenox contains a tartaric acid solubilizer to enhance absorption of dipyridamole and is taken only twice a day [29,30]. In the European Stroke Prevention Study, 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 [20].

Methods

The primary aim of the Aggrenox Prevention of Access Stenosis Trial, supported by NIDDK, is to determine whether dipyridamole given in the form of Aggrenox can prolong primary unassisted patency in patients who receive a new arteriovenous graft. Main secondary objectives are to determine whether Aggrenox prolongs overall graft patency or affects patient survival.

The design is a prospective, randomized double-blind, placebo-controlled multicenter trial of Aggrenox compared to matched placebo. The study drug and active monitoring is continued until the primary endpoint is reached (Figure 1). Further

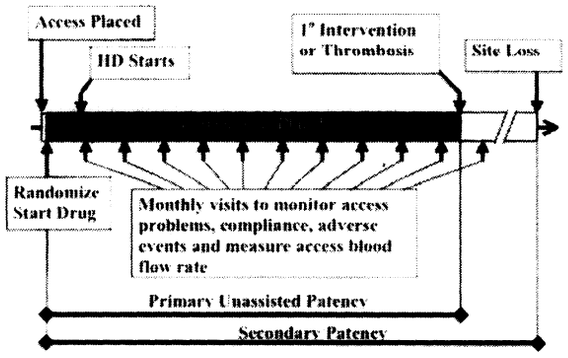

Figure 1 Overview of aggrenox prevention of access stenosis

follow-up is limited to determining whether total access site failure or death occurred prior to study closeout. Enrollment began in January 2003 and is expected to last four years, with a minimum additional follow-up of half a year for a total duration of four and half years. Five original clinical centers were expanded to include two additional clinical centers, with main study sites located in ten cities throughout the USA. (Details on the conception and organization of the DAC can be found in the article describing the concurrent DAC Fistula Trial.)

Study population

Inclusion criteria

Eligible patients will be adults who are on dialysis or expected to start hemodialysis within six months for ESRD and are scheduled to have a new arteriovenous graft (either synthetic or biograft) placed in any anatomic location or configuration for hemodialysis.

Exclusion criteria

Exclusion criteria were designed principally to exclude patients in whom Aggrenox® treatment might not be safe because of bleeding risk. They include: 1) minors <18–21 years (depending on state law); 2) women who are pregnant or breast-feeding; 3) ongoing bleeding or recent bleeding requiring a transfusion within 12 weeks of entry or a known bleeding disorder; 4) acute ulcer disease defined as a diagnosis of esophagitis, gastritis or ulcer, or initiation of treatment with a proton pump inhibitor or H2 blocker or therapy for *H. pylori* within three months of consent; 5) known allergy or adverse reaction to Aggrenox or its components; 6) required use of warfarin, dipyridamole, NSAIDs or other antiplatelet agents other than aspirin; 7) uncontrolled hypertension; 8) platelet count >75 000; 9) advanced liver disease with decompensated cirrhosis, jaundice, ascites or bleeding varices; 10) ongoing substance abuse; 11) anticipated problems with noncompliance; 12) participation in another interventional trial; or 13) patient refusal.

Enrollment and randomization

At entry, baseline demographic, clinical, quality of life and laboratory data including a complete blood count (CBC) and albumin within 45 days of entry are obtained (Table 1). Particular attention is paid to the prior access history, evidence of prior access surgeries, and presence of a central catheter. Randomization is carried out as soon as possible, but no more than two days after successful access surgery (i.e., a patent graft). Randomization is stratified by Clinical Center and by access location (forearm or alternative site). A random permuted block design is used to assure approximate balance over time. Randomization is performed centrally via the Internet using a Web browser following verification of eligibility by the Data Coordinating Center (Cleveland Clinic). Baseline albumin is a prespecified covariate in the primary analysis, but not a stratification variable.

Intervention

Following successful placement of the graft, subjects are randomized with equal allocation to either Aggrenox, one capsule twice a day, or a matched placebo. Each capsule of Aggrenox contains 200 mg of extended release dipyridamole plus 25 mg of immediate release aspirin.

Procurement, testing and distribution of study medication

Aggrenox capsules and matching placebo were provided by Boehringer–Ingelheim and shipped to McKesson Pharmaceuticals for labeling and distribution to clinical centers. The two types of capsules were identical in appearance and smell.

Double-masked design

Subjects, participating investigators and study coordinators are masked to treatment assignment. With the exception of the unique study identifier on the bottle label, all the bottles, seals, markings and labels are identical for the two types of capsules.

Follow-up observation period

The study participants are followed monthly to measure access flow rate and record access-related

Table 1 Data collected

	Baseline	First month	Monthly	Every third month
Historical				
Demographic information (age, gender, race, marital status, household size, education, occupation, work status, income, etc.)	X			
ESRD history (etiology, current dialysis status, date of first dialysis and first hemodialysis)	X			
Access history (prior AV access surgeries, prior central catheters, current access type and location)	X			
Medical diagnoses (diabetes, hypertension, cardiovascular diseases, amputations, bypass surgery, known coagulopathy, hyperlipidemia, HIV/AIDS, etc.)	X			
Medications	X	X	X	
Tobacco use	X			
Quality of life questionnaire	X			X
Exam				
Vital signs (blood pressure and pulse) (height and weight, baseline only)	X	X	X	
Periodontal disease	X			
Examine for evidence of prior AV accesses and current catheters	X			
Biochemical studies				
Hemoglobin, platelet count, albumin, creatinine, calcium and phosphorus	X	X	X	
Pre and post hemodialysis BUN (if on dialysis)		X	X	
PTH				X
Follow-up				
New study access (surgeon, graft material, location-inflow artery and outflow vein, configuration) record at randomization and confirm at first study visit		X		
Study medication compliance		X	X	
Adverse events (bleeding, transfusions, hospitalizations, other symptoms or problems)	X	X	X	
Access events or procedures (thrombosis, thrombolysis, angiogram, angioplasty, surgical revision, access symptoms, access cannulation or bleeding problems, use of vascular clamps, access infection, etc.)		X	X	
Flow monitoring (when on dialysis; see Figure 1 and, Appendix 2)		X	X	

complications, adverse drug reactions, hospitalizations and medication compliance. The schedule of data collection is shown in Figure 1 and Table 1. If a subject is not yet on hemodialysis, the patency of the access is determined by palpating for a thrill and auscultating for the presence of a bruit. Monthly follow-up is continued until one month after the primary endpoint is reached. Monthly measurement of access flow rate is used to detect a hemodynamically significant stenosis before it leads to access thrombosis. Previous studies have shown that noninvasive measurement of flow through the access can reliably predict the presence of a stenosis [31]. A drop in monthly access flow rate that meets prespecified limits triggers angiographic evaluation and repair of the access if a 50% or greater stenosis is observed.

Flow monitoring

Access flow rate is measured with the Transonic Hemodialysis Monitor HD02 (Transonic Systems Inc. Ithaca, NY, USA), which uses the saline infusion ultrasound dilution technique based on the Fick principle [32,33]. Baseline measurements of access flow are performed during two dialysis sessions, two weeks apart, within the first month that the graft is used. This is followed by monthly access flow measurements thereafter. An access flow rate less than 600 mL/min or a drop in access flow rate of 25% from baseline when the access flow rate is less than 1000 mL/min triggers a recommendation to refer the subject for angiographic evaluation (see Appendix 2).

Assessment of compliance

Compliance is assessed by patient interview and monthly pill count. Subjects are asked to return pill bottles of study medication each month.

Endpoints

Primary endpoint

The primary outcome is primary unassisted patency, defined as the time from access creation until the first occurrence of either access thrombosis

or an access procedure that is performed (or recommended) to restore access patency. Access procedures include angioplasty, thrombolysis, thrombectomy, or any surgical modification of the graft with the exception that access surgery for specific adverse consequences of graft placement (i.e., steal syndrome or congestive heart failure) within the first 30 days after creation of the access will not be considered an event for the primary composite outcome. The angiographic criteria for performing a corrective procedure is a luminal narrowing estimated by two orthogonal views to be greater than or equal to 50% of the normal diameter of the vessel. A central radiology core reviews a subset of angiograms from all Clinical Centers to determine whether the reading and recommendations meet study guidelines.

For patients who are undergoing regular hemodialysis, failure to use the new graft by six weeks after access creation will be considered access site failure and the study will be terminated. For incident patients not yet on hemodialysis, 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 will be considered to be the primary endpoint. Once the primary endpoint is reached, the study drug is discontinued.

Secondary endpoints

The main secondary outcome measures include cumulative access patency through the end of the trial, patient survival, and composite endpoints incorporating death in conjunction with access events. 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.

Primary analysis

The primary analysis of primary unassisted patency will be conducted using a Cox proportional hazards regression analysis [34] with stratification by Clinical Center and graft location (lower arm versus another site). Use of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, and the level of serum albumin at baseline will be included as prespecified covariates. The primary analysis will be conducted using an intent-to-treat strategy in which patients are retained in their randomized groups regardless of their compliance to the treatments. However, the primary 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.

Sample size and power calculations

Estimation of 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 [2,3,35,36]. Recent studies that mirror the circumstances of this study reveal one-year primary unassisted patency rates of 23 to 49% [2–4,37]. Because clinical trial participants often have a lower event rate than an unselected population, a one-year probability of primary unassisted patency of 0.46 was assumed in the study's power calculations, corresponding to a one-year probability of access failure of 0.54.

Effect size

A study by Sreedhara *et al.* found a 50% effect size for dipyridamole alone and 27% for dipyridamole plus aspirin to decrease thrombosis in new grafts [17]. 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 has also found an effect size of 41% for aspirin plus dipyridamole to decrease the percent of veins that have a stenosis compared to placebo [25]. Tempering these data is one retrospective report suggesting no effect of dipyridamole to prevent hemodialysis graft failure [38]. For secondary prevention of occlusive arterial disease (i.e., myocardial infarction and stroke), the effect size for the combination of dipyridamole plus aspirin has ranged from 18 to 36% [39]. Most of the effect is thought to be due to the aspirin and not the dipyridamole [40]. However, in a large randomized, placebo-controlled double-blind study for secondary prevention of ischemic stroke, dipyridamole alone was found to decrease the risk of stroke by 16% and the combination of aspirin plus dipyridamole further reduced the risk by 37% [20]. It is uncertain whether the pathophysiology of arterial occlusive disease is the same as vein graft stenosis, so the relevance of these studies to predict the effect size in the current trial is unknown. Based on these studies and clinical estimates of what effect size would constitute a meaningful result, an effect size of 25% was hypothesized for the primary outcome.

Power calculations

The target sample size of 1056 was selected to obtain 85% power with a two-sided Type I error rate of 5% to detect a 25% reduction in the rate of the primary outcome for Aggrenox compared to

placebo in a design with three years of uniform accrual plus a minimum of one year of additional follow-up. (After initiation of the trial, the recruitment period was extended to four years, with a minimum additional follow-up of six months to account for a slower than projected accrual rate.) Assumptions used in the power calculations included a one-year probability of access failure in the control group of 0.54 with a constant hazard rate over time, an annual loss to follow-up rate including all sources of nonadministrative censoring of 22% per patient-year, an annual medication dropout rate of 15% in the Aggrenox arm (i.e., patients randomized to Aggrenox who discontinue the medication) an annual medication drop-in rate of 1% in the Placebo arm (i.e., patients randomized to placebo who initiate use of dipyridamole or a similar medication), and use of the stopping rule described below. A treatment effect of zero was assumed during a one-month lag period immediately after randomization in order to account for postsurgical graft failures that may not be affected by the medication. The power calculations were performed using the Markov chain modeling approach of Lakatos [41]. The estimate of 22% for the rate of nonadministrative censoring was stipulated based on the results of a recently conducted multicenter trial in a similar population of hemodialysis patients [42]. Mortality, which occurred in the previous study at a rate of 17% per patient-year, is expected to be the primary reason for censoring prior to the end of the trial. Under the above assumptions, the 25% reduction in the rate of the primary outcome corresponds to a 33% increase in median primary unassisted patency from 10.70 to 14.28 months, a prolongation of graft survival that would be meaningful to the patient and clinician.

Statistical stopping rule

A Data Safety and Monitoring Board (DSMB) will periodically review the conduct of the study and patient safety. A total of five interim analyses (for a total of six analyses including the final analysis) will be performed at equally spaced information times for the primary outcome to allow the DSMB to evaluate if the study should be stopped early if either Aggrenox or the placebo interventions are proven to be superior to the other intervention, or if it becomes clear that the null hypothesis cannot be disproved under the current study design. A Lan–DeMets spending function approach will be used, with stopping boundaries derived from the Wang–Tsiatis class with shape parameters of 0 (corresponding to the O'Brien–Fleming stopping rule) [43].

Discussion

The design of this trial involved several decisions that are commonly confronted. These include selection of the appropriate study population where decisions have to be made about the potential mechanisms of action of the intervention, compromises in drug selection due to market availability and industry support, selection of endpoints that reflect the pathophysiology of the disease but may not be considered hard clinical endpoints and may represent a compromise to reduce study duration and expense. Our solutions to these issues are discussed below.

Ethics of graft study in fistula-first era

A native fistula is the recommended access for hemodialysis [44,45]. This raised a concern about the ethics of performing a large study focused on grafts. However, grafts are currently the most prevalent arteriovenous access type used in the USA [46,47]. Moreover, grafts have advantages of being easier to cannulate and can be used earlier after surgery. With fistulas, the high rate of early failure, the longer maturation time, and difficulties in cannulation can lead to increased use of central venous catheters for hemodialysis [46,48], with their attendant increased risk of sepsis and death [49,50]. If the problem of graft stenosis and thrombosis could be solved, then a graft might offer a viable alternative to a fistula. While recognizing that fistulas are preferred, the DAC Steering Committee felt that grafts would continue to be required in some patients for access and would be preferred to dialysis with a central venous catheter. Performing a single trial involving both fistulas and grafts was also considered, but discarded because the biological process leading to failure in the two types of access is thought to be different. The dilemma was resolved by performing concurrent trials to address the major problems in both types of arteriovenous access.

Risk of bleeding

The choice of Aggrenox (a combination of dipyridamole and aspirin) was a selection that was partially based on availability in the marketplace. As previously discussed, dipyridamole is the agent that is thought to prevent neointimal hyperplasia. However, its absorption from the usual preparation is erratic. Although a timed-release preparation of dipyridamole has much more predictable absorption, in the USA the timed-release preparation is only available in a formulation containing aspirin.

In order to manage the costs of the study, we recognized donation of drug and placebo from the pharmaceutical company would be important because formulation of a timed-release preparation of dipyridamole alone would be impractical and prohibitively expensive. Even formulation of matching placebo can cost upwards of a hundred thousand dollars. However, to use Aggrenox would subject patients to the potential bleeding risks of aspirin.

This raised a serious concern, because the recent VA cooperative trial studying the combination of aspirin and clopidogrel to prevent graft thrombosis in hemodialysis patients was terminated early due to increased bleeding [15]. That study found an annual hazard rate for bleeding of 0.5 episodes per patient-year on placebo and this nearly doubled with the combined antiplatelet agents [15]. Approximately 43% of these bleeds were classified as intermediate or severe. Aspirin has been shown to prolong bleeding time more in patients with end-stage renal disease compared to normal controls [51]. These results raised concern that the risk of serious bleeding with aspirin might be greater in hemodialysis patients, particularly given the extended duration of expected therapy. The few published studies of aspirin in hemodialysis patients suggest that the increased risk of serious bleeding with aspirin in hemodialysis patients will be similar to that seen in subjects without kidney disease [17,52–54]. In the study by Sreedhara *et al.*, the risk of bleeding in patients treated with either aspirin or aspirin plus dipyridamole was about two-fold more than placebo [17]. Information regarding the risk of Aggrenox in hemodialysis patients was obtained from an unpublished study carried out in the period 1986–1989 (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. Overall mortality was reduced by 40% [CI, 65%, −3%] in subjects on study medication compared to control (5.1% annual mortality compared to 8.2% in the placebo-treated control patients; unpublished results, Boehringer–Ingelheim). The reduction in mortality was primarily due to a reduction in the number of cardiac deaths. 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 (i.e., two-fold) and a significant increase in intracranial or fatal bleeding events is not expected. Considering that the risk of graft failure is 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 risks for this study.

Inclusion of people on aspirin

Despite concerns about bleeding, aspirin is commonly prescribed to patients on hemodialysis. In a recent pilot study, we found that over 25% of people obtaining a new hemodialysis access were on aspirin (unpublished, DAC Fistula Pilot Trial). Excluding people on aspirin for the study would significantly reduce the enrollment rate and limit generalizability about the effectiveness of the study drug. Consideration was therefore given to whether inclusion of subjects on aspirin would confound the study or increase the rate of adverse reactions when combined with Aggrenox. Given the low dose of aspirin in Aggrenox, it is unlikely that the addition of Aggrenox to subjects on aspirin would significantly increase their risk of bleeding. Likewise, the study by Sreedhara *et al.* suggested that the combination of aspirin plus dipyridamole would not significantly decrease the efficacy of dipyridamole to prevent access thrombosis [17]. Whether the use of aspirin in the placebo-treated subjects might decrease the rate of access failure and thereby decrease the effect size of Aggrenox is currently unknown. The few available studies of the effect of aspirin on AVG thrombosis have been mixed, with reports of increased, decreased and no effect on access thrombosis [15,17,55,56].

However, a recent randomized controlled trial of aspirin and clopidogrel found no significant benefit of antiplatelet agents [15]. After weighing the increased rate of patient enrollment against the potential confounding effect of aspirin, it was decided to include subjects on aspirin, but to carefully monitor and record its use in each patient throughout the study.

Use of prevalent versus incident grafts

An important consideration in trial design was whether to enroll subjects who already had a functioning graft (i.e., prevalent graft) or to restrict enrollment to subjects who receive a new graft (i.e., incident graft). Including people with prevalent grafts provides an immediate pool of potential subjects at the outset of the study that would speed enrollment. It also simplifies the process of identifying and recruiting subjects, because the patients are already in the dialysis unit undergoing dialysis. Moreover, people who are on dialysis or who have

suffered a prior access failure are more likely to agree to participate in the study. However, in the sentinel study by Sreedhara *et al.*, the benefit of dipyridamole was limited to patients with new grafts [17]. In prevalent grafts the process of neointimal hyperplasia that leads to access stenosis and failure will already have begun, and in some cases may have already led to access failure and the need for angioplasty. The biology of restenosis after angioplasty may be different and less amenable to therapy than the initial venous neointimal hyperplasia. Given the failure of any therapy to effectively prevent restenosis after angioplasty of arterial lesions, we reasoned that inclusion of prevalent grafts that have undergone angioplasty would significantly reduce drug efficacy. We would therefore be subjecting the prevalent patients to the potential harm of active therapy with little or no probable benefit.

Flow monitoring

Longitudinal observational studies have shown that an active access surveillance program can decrease the rate of graft thrombosis and may increase overall access survival [44,57,58]. Several approaches are used for access surveillance [44,59] and there was no uniform approach to monitoring access function across all the Clinical Centers. To promote uniformity between Clinical Centers, routine monthly flow monitoring was chosen as the standard access surveillance technique for the study. Use of regular blood flow monitoring is a unique aspect of the trial design and is not feasible in most trials looking at the progression of stenosis in other vascular beds. Its use is expected to enhance sensitivity and specificity to detect hemodynamically significant stenosis. Neointimal hyperplasia leading to access stenosis is detected by a drop in access flow rate and confirmed by angiography. This serves to confirm the mechanism of action of the study drug. Moreover, correlation of initial access flow with the subsequent rate of developing access stenosis will help address the question of whether differences in early wall shear stress contribute to the rate of neointimal proliferation.

Choice of primary and secondary endpoints

Nephrologists want a therapy that will significantly prolong cumulative graft patency and may regard primary unassisted patency as a surrogate endpoint. However, cumulative access survival would require a longer and more expensive trial. The proposed composite primary endpoint of unassisted access patency is also clinically relevant, as an optimal study medication would completely prevent the development of stenosis leading to thrombosis or the need for angioplasty. The median duration of primary unassisted patency is expected to be less than one year in the control group, leading to a high event rate, which facilitates completing the study in a reasonable time. No systemically administered drug, including dipyridamole, has been shown to prevent restenosis after balloon angioplasty. Therefore, if the study drug fails to prolong primary unassisted patency, it is unlikely that it would prolong a more distant endpoint such as cumulative graft patency that requires multiple surgical procedures or angioplasties to keep the graft open. It is anticipated that if Aggrenox prolongs primary unassisted patency, it will also prolong cumulative patency, even if the drug is stopped at the primary endpoint. Cumulative graft patency and overall patient survival will be reported and analyzed as secondary endpoints, but the study will have limited power to detect a significant difference in these endpoints.

Censoring for death in the primary analysis

In clinical trials with a primary analysis based on a time-to-event format, it is common practice to incorporate adverse clinical events, such as death, that lead to a termination of follow-up as components of a composite outcome. However, this poses a difficulty in clinical trials where the rate of these alternative adverse events in the study population is very high and not thought to be influenced by the study intervention. Including these alternative adverse events as part of a composite endpoint in the primary analysis will dilute the ability to detect an effect of the intervention on the primary endpoint of interest. The death rate in people with end-stage renal disease on hemodialysis is very high (as noted above, a death rate of 17% per patient-year is expected in this trial). If death were included in our primary analysis along with primary unassisted patency, it would account for approximately 20% of all events and thereby dilute the analysis of the effect of study drug on primary unassisted patency. Most deaths in this population are due to cardiovascular events and are not directly related to graft failure (less than 0.6% per year are due to graft failure). Therefore, because the goal of the present trial is to evaluate the effect of Aggrenox on graft patency, the Steering Committee determined that, consistent with previous studies of access survival [2–5], death should be censored as a competing risk in the primary analysis. However, because Aggrenox may affect mortality independently of access survival (e.g., by increasing bleeding or reducing cardiovascular events), composite endpoints including both mortality and access events will be analyzed as secondary outcomes.

Because of interpretational problems of censoring deaths, graphical summaries of the marginal cumulative incidence of access events will be constructed with death, transplant, and modality switches treated as competing risks [60,61]. 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.

Summary and conclusions

The Aggrenox Prevention of Access Stenosis trial is a randomized double-blind placebo-controlled trial developed by a consensus of investigators to test the hypothesis that dipyridamole in the form of Aggrenox can prevent the development of neointimal hyperplasia leading to hemodialysis graft failure. The design of the trial required consideration of ethical issues, the appropriate study population (incident versus prevalent patients), balancing risks and study effect size against drug efficacy and procurement costs, timing of study drug to maximize efficacy yet minimize risks, and choice of primary endpoint. Successful completion of the trial will address an important and costly problem in this patient population and will establish a roadmap for future trials in this area.

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Appendix 1

DAC Study Group

Boston University Medical Center: L Dember, J Kaufman, M Hawley, A Lauer, G Braden, P LeSage, R Nathan, E Holmberg, A Berkowitz, A Kennedy; *Duke University Medical Center*: A Greenberg, M Berkoben, E Kovalik, J Lawson, J Middleton, K Gitter, D Schumm, S Adams, T Cantaffa, C Best, A Quarles; *University of Iowa, Iowa City,* B Dixon, B Franzwa, J Hoballah, L Hunsicker, D Katz, S Rayhill, W Sharp, Y Wu, T Kresowik, *Peoria, IL*: T Pflederer, K DuPage, F Darras, B Ketel, K Welch, A Wounded Arrow, D Wieburg, A Banqero, C White; *Waterloo, IA*: M Slavin, D Wedeking; *Maine Medical Center*: J Himmelfarb, J Whiting, J Kane, S Freedman, R Violette, H Cyr-Alves; *University of Texas Southwestern*: M Vazquez, I Davidson, A Fenves, K Jones, L Littmon, T Lightfoot, J Middleton, G Pearl, H Quinones, R Saxena, R Toto, R Valentine, C Ying, E Anyaegbuna; *University of Alabama at Birmingham*: M Allon, M Robbin, D Gunter, B Dean, J Newsome; *Washington University*: J Delmez, R Creaghan, B Lluka; *Vanderbilt University Medical Center*: A Ikizler, P Egbert; *Wake Forest University*: M Rocco, P Daeihagh, T Hoosier, A Tuttle, D McBride; *National Institute of Diabetes and Digestive and Kidney Diseases*: J Kusek, C Meyers; *Steering Committee Chair*: H Feldman (U Pennsylvania); *Data Coordinating Center (Cleveland Clinic Foundation)*: G Beck, S Bi, J Gassman, T Greene, A Liu, M Radeva, L Tuason, B Weiss; *Data and Safety Monitoring Board (DSMB)*: N Levin (Chair), A Besarab, G Beathard, G Chertow, M Diener-West, T Louis, W McClellan, C Stehman-Breen.

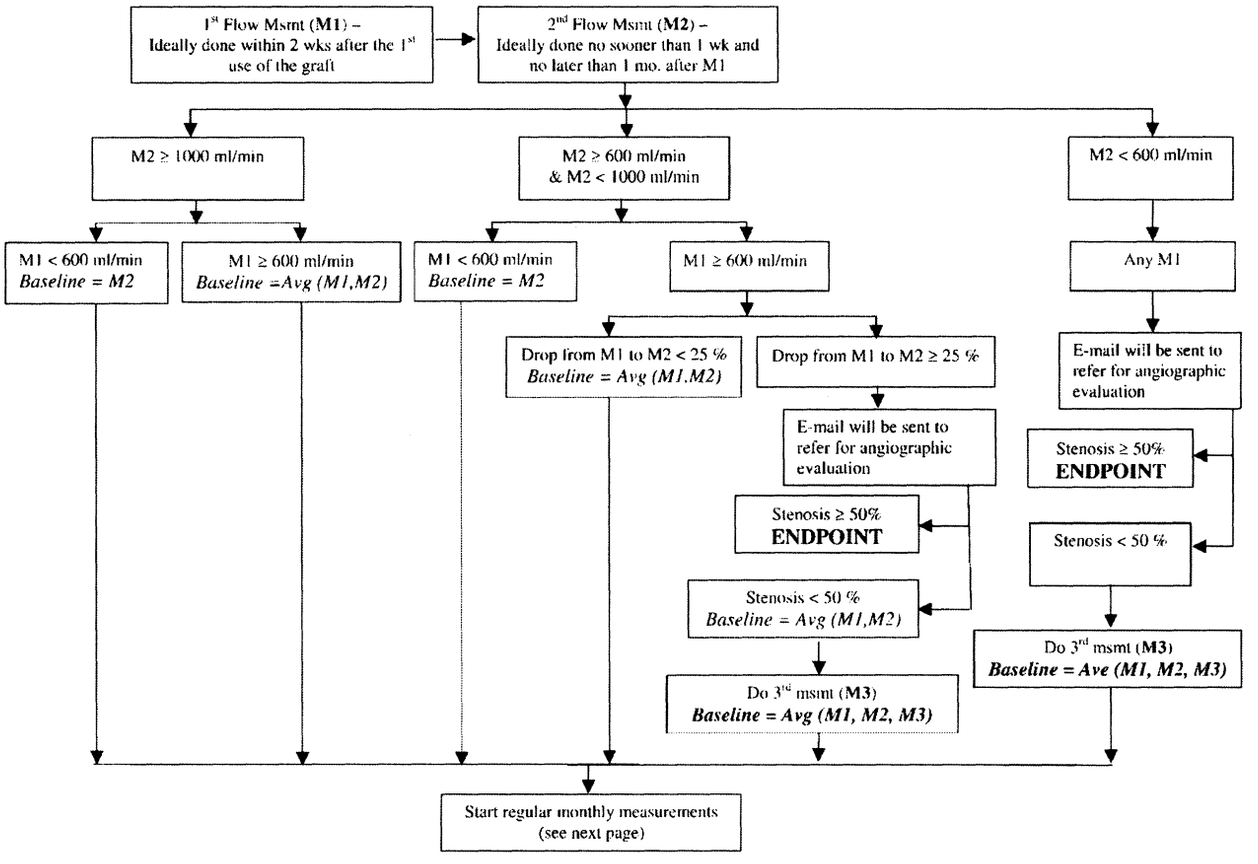

Figure A1 Flow Monitoring Algorithm. The algorithm for determining the baseline access flow rate when a patient first starts using the new graft for hemodialysis is shown along with the criteria for referral for angiography. **M1**, **M2**, and **M3** refer to the first, second and third flow measurement respectively

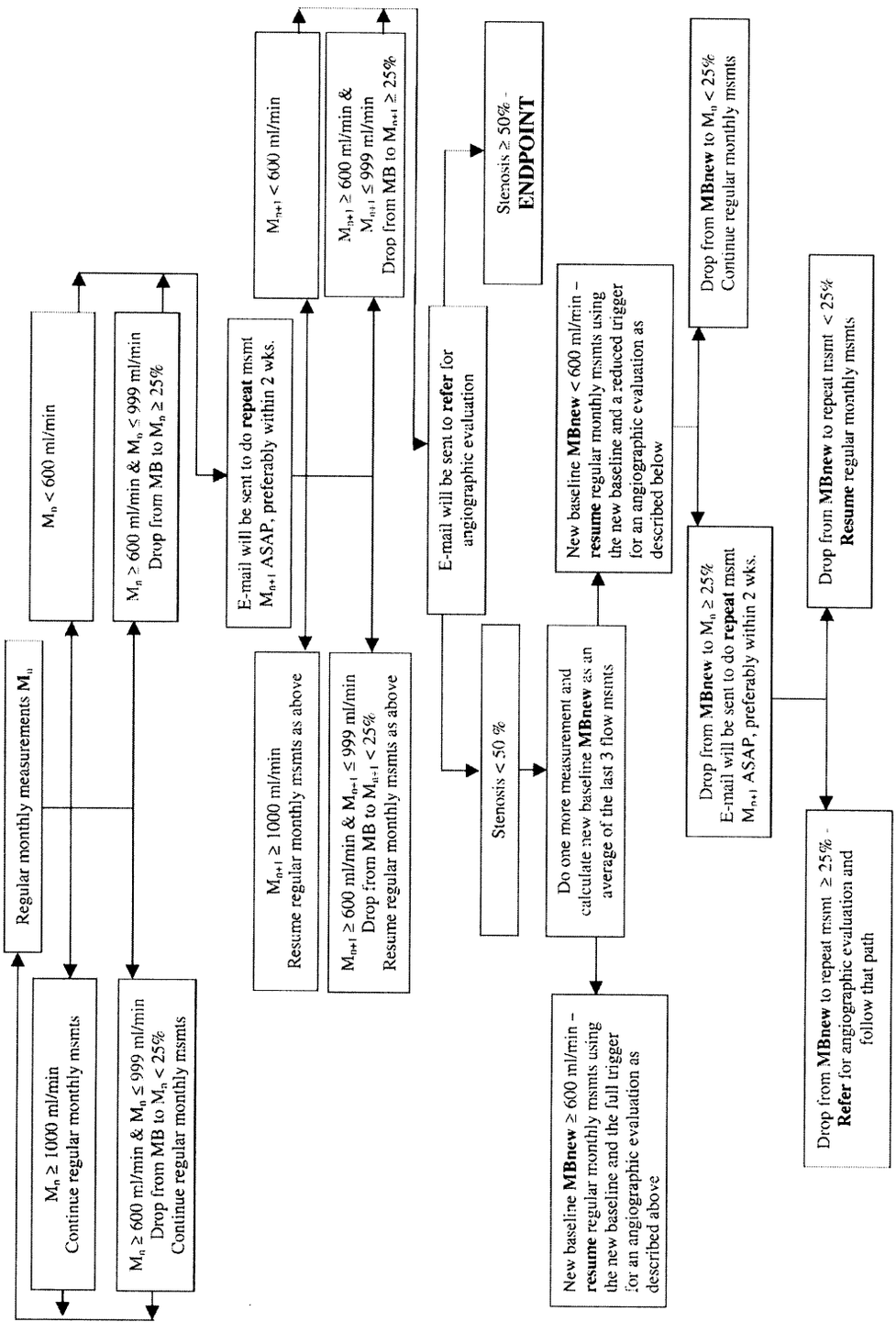

Figure A2 Flow Monitoring Algorithm (continued). The algorithm to be used for determining whether to refer a patient for angioplasty based on the results of each monthly flow measurement is shown. Mn and Mn + 1 refer to the current and subsequent monthly flow measurements, respectively. **MB**, refers to the baseline flow measurement (see Figure A1). **MBnew**, refers to a newly established 'baseline' flow measurement as shown in the algorithm.

Appendix 2

Flow monitoring

Access flow rate is measured using the saline infusion ultrasound dilution technique based on the Fick principle [32,62]. At each monthly visit the study coordinator obtains 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 are switched and two measurements of access blood flow are obtained in this reverse configuration. If the two measurements differ by greater than 10%, then a third measurement is obtained. These measurements are carried out within the first two hours after starting dialysis.

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) [11,52]. Blood pressure is recorded at the time of each access blood flow measurement and used to normalize the measured access blood flow to a standardized mean arterial pressure of 90 mmHg using the equation

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

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 [11,52].

The mean value of all the normalized access flow measurements obtained at each visit is calculated. This normalized access flow is compared to the baseline flow to determine if the subject meets criteria for access evaluation (see below). The baseline access flow rate is determined from the first two flow measurements using the algorithm shown in Figure A1. The first access flow measurement is obtained as soon as possible but no more than two weeks after starting to use the new access for dialysis. The second measurement is obtained approximately two weeks later (no sooner than one week nor more than one month after the first access measurement). Thereafter, access flow measurements are 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 Figure A2) 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 is done as soon as possible, preferably within two weeks after the first measurement that met criteria for access evaluation.

Studies with access flow monitoring have reported that, for 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 1000 mL/min is predictive of hemodynamically significant access stenosis. Based on these parameters an algorithm for the monthly surveillance of access flow rates has been developed (see Figure A2). A flow measurement will trigger consideration for an angiographic evaluation if: 1) the nQb is <600 mL/min, or 2) the nQb is <1000 mL/min and is at least 25% below the average of the first two flow measurements. If angiographic evaluation of the access reveals a stenosis of 50% or more, then a corrective procedure is undertaken to reverse the stenosis and this represents a primary endpoint of the study