CLOPIDOGREL PREVENTION OF EARLY AV FISTULA THROMBOSIS

STUDY PROTOCOL

09/07/05

CONTENT

1. BACKGROUND AND RATIONALE FOR STUDY

Maintenance of vascular access for hemodialysis is one of the major challenges in the care of the hemodialysis patient. Access-related problems are among the most frequent reasons for hospitalization in the end-stage renal disease (ESRD) population[1,2], and the cost of vascular access placement and repair in the United States currently exceeds $700 million per year[3]. The most frequent cause of access failure is thrombosis which occurs in arteriovenous (AV) grafts at a rate of 30-65% per year[4-11]. Access thrombosis usually occurs as a consequence of stenosis due to neointimal hyperplasia at the venous anastomosis[12].

The native AV fistula is the preferred type of hemodialysis vascular access because it is associated with lower rates of thrombosis and infection, reduced requirement for interventions, and lower costs compared with grafts or cuffed catheters[12,13]. Although these advantages are well recognized, the proportion of hemodialysis patients in the United States with a native fistula as the permanent access is low. The United States Renal Data System reported that in 1996 AV grafts were being used at 60 days after initiation of dialysis almost three times as often as native fistulae (50.3% vs. 17.9%)[3]. The low proportion of native fistulae has been attributed to 1) a low rate of attempted native fistula creation, and 2) early fistula failure from early thrombosis or inadequate vein maturation[14]. Because native fistulae cannot be used for dialysis for at least 6-12 weeks after creation, late referral of chronic renal failure patients to nephrologists (i.e., referral close to the time initiation of dialysis is required) has been cited as a major contributor to the low rates of attempted fistula creation[13]. The increasing percentage of diabetic or elderly patients comprising the end-stage renal disease (ESRD) population is a factor contributing to early fistula failure rates since such patients may not have veins adequate to support native fistula maturation[12,14]. Increasing the proportion of native AV fistulae among the hemodialysis population is one of the two primary goals established by the Dialysis Outcomes Quality Initiative (DOQI) Vascular Access Work Group[13].

1.1 Early Thrombosis of Native Fistulae

Thrombosis during the first days to weeks following access creation (early thrombosis) occurs in 12-30% of new native fistulae[5,15,16]. Unlike thrombosed grafts for which restoration of patency can be achieved in >85% of cases with radiological or surgical intervention[12], thrombosis of a native fistula usually results in abandonment of the access. From a technical standpoint, radiological declotting is considerably more difficult for fistulae than for grafts, and surgical thrombectomies of native fistulae are often followed by immediate or early re-thrombosis[17,18]. Many interventional radiologists and vascular surgeons will not attempt declotting procedures in native fistulae. In addition, prophylactic repair of access stenosis, a strategy which has been shown to reduce vascular access thrombosis rates[19,20], is generally not applicable to the problem of early native fistula thrombosis, since early thrombosis occurs before such monitoring methods are implemented (i.e., before the fistula is used for dialysis).

1.2 Strategies to Prevent Early Thrombosis of Native Fistulae

Several approaches have been considered to improve the early patency of native fistulae. Pre-operative examination using venography, ultrasound, or arteriography, may identify the best location for creation of native fistulae in patients with vasculature that is suboptimal for supporting fistula maturation[21]. While such studies are utilized in many centers, there is not strong evidence that their use increases the number of functioning fistulae, and, in fact, performance of these diagnostic tests may discourage attempts at fistula creation among patients with a reduced but potential likelihood of attaining a suitable native fistula.

Identification of risk factors for fistula thrombosis has been attempted by several investigators[23-27]. Many of the predictors of thrombosis such as age, gender, diabetes, race, low blood pressure, and longer dialysis treatment times are both controversial and not readily amenable to modification. Consistent associations between laboratory abnormalities and vascular access thrombosis have not been demonstrated in the few studies examining them[22,23]. Thus, at present, targeting specific risk factors for modification is not a feasible approach to the problem of early fistula thrombosis.

Similarly, several factors have been identified as predicting adequacy of AV fistulas. Miller et al[14] found that overall only 47 (46.5%) of 101 fistulas placed over a two year period matured adequately to be used at a blood flow $\geq$350 ml/min. The adequacy was lower if age $\geq$65 years old (30.0%, P=0.03), in diabetics (35.0%, P=0.061), and if BMI $\geq$27 (34.5%, P=0.07). Furthermore, the adequacy of forearm fistulae were particularly poor in women (7%), age $\geq$65 years old (12%), and diabetics (21%), and the authors recommended the creation of upper arm fistulae in such patients. They felt that their lower overall rates of access maturation were due to attempting fistulae in patients who previously might have received grafts. Although this study indicates that the use of the upper arm may increase the development of adequate fistula, it will be difficult to achieve the rates of fistula use suggested in current guidelines.

Based on what is known about the role of platelets in the response to endothelial injury, pharmacologic inhibition of platelet aggregation and/or activation is an appealing approach to early fistula failure. The response to endothelial injury consequent to the surgical creation of the AV fistula is likely to be an important factor in the development of early fistula thrombosis. It is recognized that the greatest rate of fistula loss occurs within the first three months of surgery[5,14]. Although some of this loss may be due to technical factors such as the use of inadequate veins or severe atherosclerosis in the feeding artery, development of thrombosis as a consequence of endothelial injury may also be important. The efficacy of antiplatelet agents in the prevention of early fistula thrombosis suggests that endothelial injury does play a role. The results of several small studies of antiplatelet agents in preventing native fistula thrombosis are discussed in the section that follows.

1.3 The Use of Anti-Platelet Agents to Prevent Thrombosis of Native Fistulae

Studies evaluating the efficacy of antiplatelet agents for the prevention of native fistula thrombosis are summarized in Table 1.1[27-35]. Ticlopidine 250 mg twice a day, microencapsulated aspirin 1 g/day or 500 mg three times a day, and sulfinpyrazone 200 mg three or four times a day have all been shown to be effective in studies lasting from 1 to 3 months. These studies only included patients receiving new primary native fistulae and the drugs were started up to 3 days before surgery. Ticlopidine is the agent most commonly used in these studies and Gröntoft et al have recently reported the largest trial of ticlopidine use to prevent early fistula failure[33]. Two hundred thirty-two patients were randomized to receive ticlopidine 250 mg twice a day or matching placebo beginning 3-7 days prior to scheduled native fistula creation and continuing for 28 days postoperatively. The thrombosis rate was 19% in the placebo group and 12% in the ticlopidine group (P=0.101). The lack of a statistically significant effect of ticlopidine in this study may have been due to a much lower rate of thrombosis in the placebo group than had been previously reported and an insufficient number of study subjects. The authors performed a pooled analysis of all studies of ticlopidine use in patients with native fistulae, and found a 25% thrombosis rate in the placebo group compared to a 12% thrombosis rate in the ticlopidine-treated patients indicating a significant ($p<0.001$) benefit of ticlopidine. One important deficit of the studies of early fistula patency is that none reported specific data on whether the fistulae matured sufficiently to serve as hemodialysis access.

Table 1.1: Studies of Antiplatelet Agents in Native Fistulae

Reference	N (Rx/Control)	Treatment	Treatment Duration	Thrombosis Rate Treatment	Thrombosis Rate Control
Andrassy et al[28]	45/47	Aspirin 1000 mg/day	4 weeks	4%	23%
Janicki et al[29]	20/6	Sulfinpyrazone 200 mg tid	3 weeks	0%	15%
Michie et al[30]	7/5	Sulfinpyrazone 200 mg qid	3 months	29%	40%
Albert[31]	17/19	Aspirin 500 mg tid vs Sulfinpyrazone 200 mg tid	6 weeks	6% (ASA)	0%(Sulf)
Gröntoft et al[32]	19/17	Ticlopidine 250 mg bid	4 weeks	11%	47%
Gröntoft et al[33]	129/131	Ticlopidine 250 mg bid	4 weeks	12%	19%
Fiskerstrand et al[34]	6/9	Ticlopidine 250 mg bid	1 month	6%	9%
Janicki et al[35]	11/15	Ticlopidine 250 mg bid	3 weeks	9%	27%

Although most studies have shown a positive effect of antiplatelet agents in preserving the patency of native fistulae, Kooistra et al were unable to demonstrate a benefit with low-dose aspirin[36]. They performed a randomized crossover study of the effect of aspirin, 30 mg daily, on thrombovascular events in 68 patients. The type of hemodialysis access is not specifically described. It is referred to as "dialysis fistula" but it is unclear if the patients had native fistulae. Seven access thromboses occurred during the placebo period and 10 during aspirin treatment (χ^2=0.41, p>0.5). One important design difference between this study and the positive antiplatelet studies is that this study included patients with an existing access rather than patients undergoing surgical placement of a new fistula.

Combining all the studies of antiplatelet agents in patients with new native fistulae in which there was a placebo control group, the thrombosis rate in the control group was 58 of 231 (25%), while that in the treatment group was 25 of 237 (11%). The difference in thrombosis rates is significant (χ^2= 17.071, p<0.0001). These studies suggest that short-term use of antiplatelet agents such as aspirin, sulfinpyrazone, or ticlopidine beginning 1-3 days prior to surgery and continuing for one to three months may increase the immediate patency of native fistulae.

1.4 Selection of Clopidogrel for the Study

The results of the studies summarized above provide compelling support for a well-designed, sufficiently powered trial of antiplatelet therapy for the prevention of early fistula failure. Our selection of clopidogrel as the antiplatelet agent for use in the proposed study is based on the following considerations. Clopidogrel, like ticlopidine, is a thienopyridine derivative which selectively and specifically interferes with ADP-mediated platelet activation causing an irreversible, non-competitive inhibition of platelet function. Release of platelet granule constituents, platelet-platelet interactions, and platelet adhesion to the endothelium and atheromatous plaque are all inhibited by the drug. Unlike ticlopidine, clopidogrel is not associated with hematologic toxicity, and, for this reason, has essentially replaced ticlopidine in clinical practice. Although a beneficial effect of aspirin has been suggested in a few studies of fistula thrombosis28, and demonstrated definitively for specific cardiovascular indications, a study by Sreedhara et al37 raises concerns about its use in the prevention of vascular access thrombosis. In this double blind study comparing rates of thrombosis of polytetrafluorethylene (PTFE) grafts among patients randomized to treatment with dipyridamole, aspirin, dipyridamole plus aspirin, or placebo, thrombosis rates in patients with new accesses were higher in the aspirin group than in the placebo group (relative risk 1.99, 95% CI 0.88-4.48, p=0.33). Although the difference was not statistically significant, the unexpected finding of a trend toward an adverse effect of aspirin is noteworthy. Subsequent in vitro studies demonstrating that platelet derived growth factor-induced vascular smooth muscle proliferation was enhanced by aspirin lend support for the clinical observation38,39.

1.5 Toxicities of Clopidogrel

Although antiplatelet therapy may be useful in preventing access thrombosis clinicians have been wary of using such agents because of the potential bleeding consequences. Patients with end-stage renal disease undergoing dialysis may have an increased incidence of hemorrhagic complications. This increase in bleeding risk is generally attributed to platelet dysfunction40. Data on the rate of spontaneous bleeding complications in the modern dialysis era are lacking but are likely to be lower than the rates reported in older literature when less efficient dialyzers and higher doses of heparin were used. Additionally, bleeding rates may have been further reduced by the correction of severe anemia with the use of recombinant erythropoietin41. In the previously cited studies of the use of antiplatelet agents in the prevention of access thrombosis, the rates of bleeding were 0-19%, but in none of the studies were the rates greater than in placebo-treated patients23,28,31,32,35,37,42.

The major toxicity data regarding clopidogrel come from the CAPRIE trial, a large randomized, blinded study comparing clopidogrel to aspirin in the prevention of vascular end-points in patients with symptomatic atherosclerotic disease43. 9,599 patients received clopidogrel 75 mg daily and 9586 patients received aspirin 325 mg daily for a mean duration of follow-up of 1.91 years. The results demonstrated a significant relative event rate reduction of 8.7% in favor of clopidogrel. Rash (6.02% vs 4.61%) and diarrhea (4.46% vs 3.36%) were more common in the clopidogrel group, while indigestion/nausea/vomiting (17.59% vs 15.01%), gastrointestinal hemorrhage (2.66% vs 1.99%), and abnormal liver function tests (3.15% vs 2.97%) were more common in the aspirin group. Study drug was permanently discontinued due to rash more commonly in the clopidogrel group (0.90% vs 0.41%), while indigestion/nausea/vomiting (2.41% vs 1.90%) and gastrointestinal hemorrhage (0.93% vs 0.52%) more commonly resulted in permanent discontinuation of study medication in the aspirin group. No differences in the incidence of severe neutropenia (granulocyte count <450/mm3) (0.05% and 0.04%) and thrombocytopenia (platelet count <100,00/mm3) (0.26% vs 0.26%) were noted comparing clopidogrel to aspirin. The results of this large trial indicate that clopidogrel is at least as safe as medium-dose aspirin.

It should be noted that the CAPRIE study excluded patients with severe renal disease, although this criterion was not explicitly defined. In a study of 16 patients with renal insufficiency (eight with creatinine clearance of 5-15 ml/min and eight with clearance of 30-60 ml/min), receiving clopidogrel 75 mg daily for eight days, renal clearance of clopidogrel decreased with declining renal function44. However the Area Under the Curve also declined due to increased extrarenal clearance. The bleeding time was prolonged by a factor of 2.2-2.4 in both groups. One patient developed a subconjunctival hemorrhage that was attributed to coughing by the investigator. These limited data indicate that there is not an excessive risk from clopidogrel usage in patients with chronic renal failure and dose adjustments may not be necessary. The Department of Veterans Affairs performed a trial of combination aspirin and clopidogrel in patients with hemodialysis grafts. The study was stopped on the recommendation of the Data Monitoring and Safety Board because of an increased bleeding risk in the active treatment group that was felt to outweigh the reduction in the rate of access thrombosis. It may be that the well-known gastrointestinal toxicity of aspirin, combined with the additional platelet inhibitory effects of clopidogrel, led to an increase in gastrointestinal bleeding. These results should not be construed to indicate that single antiplatelet agents alone, such as clopidogrel, would not be efficacious in inhibiting the development of fistula thrombosis without causing significant toxicity.

Thrombotic thrombocytopenic purpura (TTP) has been reported rarely with use of clopidogrel. TTP was not seen during clopidogrel's clinical trials (included >11,300 patients

worldwide) but was reported in postmarketing experience at a rate of 4 cases per million patients exposed.

1.6 Rationale for Performing the Study

Arguments for increasing the prevalence of native AV fistulae among the United States hemodialysis population have been convincingly presented by numerous experts in the fields of vascular access, dialysis outcomes, quality of life, and health economics. In order to achieve the DOQI goal of native fistulae in 40% of patients, multifaceted strategies directed at both promoting earlier referral of chronic renal failure patients for dialysis access placement and reducing the primary failure rate of native fistulae are required. Anti-platelet agents are gaining increasing use in the treatment of cardiovascular disease and their safety and efficacy are well-accepted. Given the promising results of several small, single-center trials evaluating the effect of such agents on early patency of new native fistulae[28-35], a large, well-designed, randomized, controlled, multicenter trial is warranted. By employing readily administered pharmacologic therapy for a short period of time the prevalence of functioning native fistulae in the hemodialysis population may be substantially increased.

2. OBJECTIVES AND DESIGN

2.1 Objective

The objective of the study is to determine whether clopidogrel reduces the early failure rate of native AV fistulae.

2.2 Design

The trial is a randomized, double-blind, placebo-controlled multi-center trial with a parallel treatment design. Patients with chronic renal failure who are on chronic hemodialysis or anticipated to begin chronic hemodialysis within 6 months will be randomized within one calendar day following creation of a new upper extremity native AV fistula to receive either clopidogrel or placebo for six weeks. Randomization will be on a 1:1 active drug:placebo allocation, and will be stratified by Clinical Center and location of AV fistula (forearm vs upper arm). Both patients and study personnel will be masked to treatment assignment. The sample size is 1284 patients, to be recruited at seven Clinical Centers over a 4-year period. Study drug administration will begin within one calendar day following native AV fistula creation and continue for 6 weeks following surgery. The primary outcome measure is fistula patency at the end of the 6-week study drug administration period. A secondary outcome measure is fistula suitability for dialysis.

A follow-up evaluation will be conducted six weeks following creation of the AV fistula. Fistula patency (primary outcome) will be ascertained at that visit. Contact will be made with the patient and/or dialysis unit on a monthly basis thereafter to obtain data related to the fistula suitability for dialysis outcome. All randomized patients who undergo creation of a native fistula will be followed regardless of whether or not they remain on their assigned treatments. Participation in the study will end once the fistula suitability outcome has been ascertained. Fistula suitability outcome ascertainment will occur during the fourth month following fistula creation for those patients who are either on chronic hemodialysis at the time of fistula creation or begin hemodialysis within 4 months of fistula creation. If dialysis is not initiated within 4 months of fistula creation, ascertainment of fistula suitability for dialysis will occur during the first month

of hemodialysis. If the fistula has not been used at the time of the suitability assessment, but may be used in the future, the patients will continue to be followed until it is determined whether the fistula is actually used.

3. ENROLLMENT, RANDOMIZATION, AND BLINDING

Patients will be recruited from the hemodialysis and chronic renal failure populations of the participating Clinical Centers. The study coordinator will be in regular contact with the nephrologists and vascular access surgeons at the participating facilities to identify patients who will be undergoing upper extremity native fistula creation. Potential subjects should be approached prior to the scheduled surgery date and enrolled in the study if eligibility criteria are met and informed consent is obtained. Enrollment will be permitted up to one calendar day following fistula creation. Patients considering enrollment in the trial will be given the consent form and other information, and permitted time to decide whether to enroll in the trial. The consent statement must be signed before performing any additional laboratory studies to determine eligibility. Patient enrollment and baseline data collection will take place within 45 days prior to randomization. If surgery is delayed such that it occurs more than 45 days after baseline data collection, review of eligibility criteria must occur and new baseline laboratory data must be obtained. If surgery is rescheduled for more than 90 days after the patient signed the informed consent, in addition to obtaining new baseline data, the informed consent process, (including signing the informed consent document) will be repeated.

3.1 Inclusion Criteria

The inclusion criteria are designed to enroll patients who will be undergoing creation of a new AV fistula. It is not required that the fistula be the patient's first dialysis access. Only patients undergoing fistula creation in the upper extremity will be included since the number of patients undergoing lower extremity native fistula creation is small, and upper and lower extremity fistula thrombosis rates may differ.

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. Planned creation of native upper extremity AV fistula.
5. The patient is not on aspirin, or the patient is on aspirin but has not had a myocardial infarction or a cerebrovascular accident within the past 12 months.
6. The patient is expected to stay at a participating dialysis facility for at least 6 months.
7. The patient's physician(s) will allow the patient to participate.
8. Ability to give informed consent.

3.2 Exclusion Criteria

The exclusion criteria are designed to exclude the following: 1) patients for whom the administration of antiplatelet agents may be unsafe, and 2) patients taking other anti-thrombotic agents or antiplatelet agents in whom it is unsafe to discontinue the medications during the six week study drug administration period.

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, breastfeeding, 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. A condition which prohibits discontinuation of anticoagulant drugs, aspirin, or nonsteroidal anti-inflammatory drugs during the six week study drug administration period. Use of heparin during dialysis is allowed.
7. Required use of oral or intravenous glucocorticoids at a dose greater than the equivalent of prednisone 15 mg per day during the six week study drug administration period.
8. Current unstable angina.
9. Required use of clopidogrel.
10. Known hypersensitivity to clopidogrel.
11. Medical considerations making anti-platelet therapy dangerous.
12. Current uncontrolled hypertension with systolic blood pressure in excess of 200 mm Hg or diastolic blood pressure in excess of 115 mm Hg at the time of enrollment.
13. Baseline platelet count less than 75,000/mm^3.
14. Known advanced liver disease with decompensated cirrhosis, jaundice, ascites or bleeding varices.
15. Current problem with substance abuse.
16. Concurrent participation in another medical intervention trial.
17. Anticipated non-compliance with medical care based on physician judgment.
18. Patient refusal.

3.3 Randomization

Patients enrolled in the study will be randomized following creation of the new upper extremity native fistula. Randomization will be performed post-operatively in order to avoid randomization of patients for whom a planned fistula does not actually get created. Randomization will be performed via the Internet using a web browser following verification of eligibility by the Data Coordinating Center.

Randomization will be based on a 1:1 study drug: placebo distribution. The random treatment assignment will be stratified by Clinical Center and by location of AV fistula (forearm versus upper arm). Stratification by Clinical Center is necessary because of possible regional differences in clinical practices. Within a Clinical Center, the predominant variables affecting outcomes will be related to the vascular surgeon placing the access. However, because of the large number of surgeons likely to be creating fistulae in each Clinical Center, it is impractical to stratify by surgeon. Stratification by location of fistula is necessary because of differences in

failure rates between forearm and upper arm fistulae. Treatment assignment codes will be made using random permuted blocks within each stratum.

3.4 Blinding

Treatment assignment will be masked to both patients and study personnel. Matching clopidogrel and placebo will be provided by Bristol-Myers Squibb and Sanofi-Synthelabo. One potential source of unblinding is prolonged hemostasis time after removal of dialysis needles at the termination of dialysis. Although it is possible that clopidogrel may prolong bleeding time and result in difficulty achieving hemostasis after removing dialysis needles, this should be an issue in only the subset of patients already receiving hemodialysis prior to enrollment in the study. Based on the demonstration that clopidogrel did not prolong the time to hemostasis in a group of nine hemodialysis patients[45], we do not expect inadvertent unblinding due to such events.

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 possible. Given the short duration of study drug administration, we anticipate that the number of patients requiring unblinding will be small.

4. STUDY TREATMENT PLAN

4.1 Study Visits and Patient Contacts

Patients will be evaluated at three study visits. See Section 5 for details regarding the data collected at each visit. The first study visit will be a screening evaluation, during which eligibility will be assessed, and informed consent and baseline demographic/laboratory data will be obtained, and quality of life will be measured. It is preferred that this visit occur prior to creation of the new native fistula; however, enrollment will be permitted up to one calendar day following fistula creation. Randomization for treatment assignment will be performed following fistula creation surgery after verification that a fistula was created. If the surgeon reports that the fistula thrombosed in the operating room or in the recovery room, the patient should not be randomized. Randomization and study drug delivery to the patient must occur such that study drug administration can begin within one calendar day following fistula creation surgery. Contact will be made either in person or by telephone on the first working day following fistula creation surgery to verify that the patient has started the study medication and to remind the patient to take the medication as directed. During this contact, the study coordinator or investigator will ensure that the patient knows how to contact study personnel if questions arise or in the event of adverse events. If a patient is not randomized because of failure to create a native fistula, the patient will be informed that he/she will not be participating in the study.

The second study visit will occur six weeks after fistula creation (coinciding with completion of study drug). At this visit the patency of the fistula will be determined by physical examination (i.e., presence of bruit). Adverse events and side effects of treatment will be reviewed. Study drug pill count will be performed. A quality of life questionnaire will be completed [46-47].

After the six-week study visit, additional data will be collected until the fistula suitability outcome is ascertained. The data will be collected through contacts with study subjects, their physicians, their dialysis units, and other sources as needed.

The third study visit will occur following ascertainment of the fistula suitability outcome. At this visit, a quality of life questionnaire will be completed [46-47], procedures performed on the fistula will be documented, and adverse events will be reviewed. The patient will be informed that participation in the study has ended. Ascertainment of fistula suitability will occur during the fourth month following fistula creation for patients who are on dialysis within 4 months of fistula creation or during the first month of dialysis for patients who start dialysis > 4 months following fistula creation. The fistula suitability outcome will not be ascertained for those patients who do not start hemodialysis during the study period. If the fistula has not been used at the time of the suitability assessment, but may be used in the future, the patients will continue to be followed until it is determined whether the fistula is actually used.

4.2 Study Drug Administration

Study drug will consist of identical tablets containing either clopidogrel 75 mg or placebo. The supply of study drug will be provided to the patient following treatment group assignment. Patients will be instructed to take the first dose of study drug by mouth - clopidogrel 300 mg (4 pills) or placebo (4 pills), within 1 calendar day following fistula creation surgery. After that, the patient will take clopidogrel 75 mg (1 pill) or placebo (1 pill) daily. Study drug will be continued until 6 weeks after fistula creation surgery.

4.3 Initiation of Fistula Use

There are no data on the optimal time of fistula maturation and therefore decisions about when to initiate use of the new fistula will be left to the patient's nephrologist and/or vascular surgeon.

4.4 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.

4.4.1 Bleeding

Bleeding will be classified as minor, intermediate, major, life-threatening or fatal. Minor bleeding events are episodes of bleeding that do 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 requires 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, epistaxis, 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 measure 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.

4.4.2 Surgery or Other Invasive Procedures

If the patient requires elective surgery or other invasive procedures with a bleeding risk, 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. Because of the short duration of study drug administration, elective procedures should be delayed until completion of study drug if such a delay is felt to be safe and not burdensome to the patient. If the patient requires emergent surgery where there is risk for bleeding (e.g., neurosurgery, hip replacement, abdominal surgery), study medication should be discontinued and consideration should be given to revealing the medication code and administering platelet transfusion if the patient has been receiving active drug.

4.4.3 Concomitant Medications

Patients should not receive any other antiplatelet or antithrombotic agents other than intra-dialytic heparin during the 6 weeks following fistula creation. Specifically, aspirin, non-steroidal anti-inflammatory drugs, dipyridamole, sulfinpyrazone, and warfarin are not to be used. Oral or intravenous glucocorticoids at a dose greater than the equivalent of prednisone 15 mg per day should not be used. Acetaminophen, codeine, or other analgesics not containing aspirin or NSAIDs may be used for pain. If the proscribed agents are required (e.g., warfarin for deep venous thrombosis or atrial fibrillation, aspirin for new cardiovascular event) during the period of study drug administration, study medication should be discontinued and the patient should continue to be followed. For patients on aspirin prior to enrollment, the aspirin should be discontinued seven days prior to fistula creation surgery and resumed after the 6 week study drug administration period.

4.4.4 Discontinuation of Therapy

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

1. Removal from hemodialysis because of transplantation, recovery of renal function, or use of other dialysis modality.
2. A medical event which contraindicates continued use of an antiplatelet agent during the six week study drug period.
3. Any bleeding episode which contraindicates the continued use of antiplatelet agents during the six week study drug period. Such events include, but are not limited to, major bleeding defined as confirmed retroperitoneal, intra-articular, or cerebral hemorrhage or any bleeding

episode resulting in a 2 g/dl decrease in the hemoglobin concentration and requiring hospitalization or transfusion.
4. An adverse event attributed to the study medication without other etiology that does not respond to medical management.
5. An acute cardiovascular event requiring antiplatelet therapy.
6. Native fistula thrombosis during the six-week study drug administration period. Thrombosis must be confirmed by a member of the study team or by the patient's vascular surgeon. Participation in the study will end 30 days after discontinuation of the study drug if fistula patency is not restored by thrombectomy or thrombolysis. If fistula patency is restored, the patient will remain off study drug, but will remain in the study until the fistula suitability for dialysis is ascertained.

4.4.5 Events Leading to Withdrawal from the Study

A patient will be withdrawn from the study for the following reasons:
1. The patient leaves the participating dialysis unit and cannot be followed in another dialysis unit.
2. The patient is judged lost to follow-up after repeated attempts to contact have failed.
3. Withdrawal of consent.
3. Death.

4.4.6 Fistula Thrombosis Within the First Six Weeks Following Fistula Creation Surgery

If fistula thrombosis occurs prior to randomization, the patient should not be randomized to treatment group and study participation will end. If fistula thrombosis occurs after randomization, study drug will be discontinued. Study drug should not be discontinued for thrombosis unless thrombosis is confirmed by a member of the study team or by the patient's surgeon. The duration of study participation after fistula thrombosis will depend on whether fistula patency is restored. If fistula patency is not restored, study participation will end 30 days after the study drug is discontinued. If fistula patency is restored, the patient will remain off the study drug, but participation in the study will continue until the ascertainment of fistula suitability for dialysis.

4.5 Study Completion

Participation in the study will end once the fistula suitability for dialysis outcome has been ascertained. This ascertainment will be completed by 150-180 days after fistula creation for patients already on chronic dialysis at the time of fistula creation and for patients who begin chronic dialysis within 120 days after fistula creation. For patients who start chronic dialysis >120 days following creation of the AV fistula, ascertainment of fistula suitability for dialysis will be completed by 30-60 days after the start of chronic dialysis. However, if the fistula has not been used at the time of the suitability assessment, but may be used in the future, the patients will continue to be followed until it is determined whether the fistula is actually used. For patients who do not start hemodialysis by the end of the study period, the fistula suitability outcome will not be ascertained and completion of study participation will coincide with the end of the study.

If fistula thrombosis occurs prior to the ascertainment of fistula suitability for dialysis, and if fistula patency is not restored, study participation will end at the time of fistula thrombosis or 30 days after study drug discontinuation, whichever comes later. Fistula thrombosis must be confirmed by a member of the study team or the patient's vascular surgeon. If fistula thrombosis occurs prior to the ascertainment of fistula suitability for dialysis, and if fistula patency is restored, participation in the study will end once the fistula suitability for dialysis outcome has been ascertained.

Data collection after study participation has ended will include hospitalization and mortality data obtained from national databases while the study is on-going and for up to five years after the study has ended.

5. DATA COLLECTION

5.1 Baseline Data

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

1. Demographic Data – age, gender, racial/ethnic background.
2. Medical History – cause of ESRD, diabetes mellitus, hypertension, myocardial infarction, angina, congestive heart failure, cerebrovascular accident or transient ischemic attack, claudication, amputation, smoking history, deep venous thrombosis or pulmonary embolism, nephrotic syndrome, significant bleeding event within past year, peptic ulcer disease.
3. Height and weight (for determination of body mass index).
4. Access History – number, type, and location of any previous accesses.
5. Dialysis History – date of initiation of chronic dialysis, if currently on dialysis.
6. Current Medications
7. Blood Pressure (sitting) – For patients already on dialysis, this should be a pre-dialysis, mid-week measurement.
8. Laboratory Data – CBC. For patients on dialysis, the blood should be drawn pre-dialysis. Laboratory tests should be done no longer than *45* days prior to randomization.
9. Quality of life

5.2 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 (30 ml) 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.

5.3 Six Weeks After Fistula Creation

1. Fistula Anatomy – date of surgery, site of anastomosis (e.g., wrist, elbow), inflow artery, outflow vein.
2. Fistula Patency –presence of bruit throughout systole and diastole ≥8 cm proximal to the arteriovenous anastomosis
3. Current Medications
4. Intercurrent /Adverse Events – drug reactions, side effects, hospitalizations, death, access procedures (fistulogram, angioplasty, thrombectomy, conversion to graft, ligation of draining veins), abnormal laboratory values, or other complications. The occurrence of any such events should be reported as close to the time the event occurred as possible;

however, the review at this study visit should minimize the possibility that such events go unrecognized or unreported. Patients will be instructed at enrollment to inform study personnel immediately if a bleeding event occurs.

5. If dialysis was initiated via the new fistula prior to this six-week study visit the date of initiation of dialysis should be recorded.
6. Procedures performed on fistula (fistulogram, angioplasty, thrombectomy, conversion to graft, ligation of draining veins), and dates of such procedures.
7. Study Drug Use – reason for and duration of study drug interruption. Remaining study drug should be returned at this visit and pill count performed.
8. Quality of life

For patients with fistula thrombosis and no restoration of patency during the six week study drug administration period, all of the above data (#'s 1-8) will be collected at the earlier of the following: six weeks after fistula creation or at the end of study participation (30 days after discontinuation of study drug).

5.4 Follow-up Data

After the six-week study visit, contact will be made by the study coordinator with study subjects, their physicians, their dialysis units, and other sources on a monthly basis to capture data on interim events and to ascertain secondary outcomes. The data to be collected include:

1. Date of first cannulation of fistula.
2. Date at which fistula is used for four weeks of consecutive dialysis treatments.
3. Minimum dialysis machine blood flow rate during the 12 dialysis sessions prior to study completion. The minimum blood flow rate should be determined from the blood flow measurements recorded after the first hour and before the last 15 minutes of the dialysis session. Study completion will occur 5 months after fistula creation for patients who are on dialysis at the time of fistula creation or start dialysis within 4 months of fistula creation. Study completion will occur 4 weeks after dialysis initiation for patients who start dialysis >4 months after fistula creation. However, if the fistula has not been used at the time of the suitability assessment, but may be used in the future, the patients will continue to be followed until it is determined whether the fistula is actually used.
4. Procedures performed on fistula (fistulogram, angioplasty, thrombectomy, conversion to graft, ligation of draining veins), and dates of such procedures.
5. For patients not on chronic dialysis prior to creation of the fistula – date of first dialysis.
6. Intercurrent/Adverse Events - bleeding events and hospitalizations during the 30 days following end of study drug administration period. Death during the period of study participation.
7. Quality of life

For patients with fistula thrombosis and no restoration of patency during the six-week study drug administration period, quality of life data is collected as indicated in item 7.

Data collection after study participation has ended will include hospitalization data and mortality data obtained from national databases while the study is on-going and for up to five years after the study has ended.

5.5 Quality Control at the Clinical Centers

Clinical procedures will be done following the Manual of Operations. Data will be edited by automated programs at the time of data entry. At site visits, a team will check each clinical center's adherence to protocol and its patient recruitment, retention, and compliance. During a

data audit portion of each site visit, team members will compare data in the study database with source documentation for a random subset of the patients.

Bleeding is the major expected risk of therapy with clopidogrel. 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. PRIMARY OUTCOME MEASURE

The primary outcome will be unassisted patency six weeks after fistula creation. Fistula patency will be determined by physical examination of the fistula performed by trained study personnel. The fistula will be classified as patent if a bruit is present throughout systole and diastole. The bruit must be detectable along the vein at least 8 centimeters proximal to the arteriovenous anastomosis. In a quality control subset of patients the outcome will be independently assessed by at least one trained member of the study team and a second person.

The fistula patency outcome will be ascertained at 6 weeks in all patients except those in whom study drug was discontinued because of fistula thrombosis prior to six weeks. To allow patients with fistula thrombosis and no restoration of patency to complete study participation within 30 days of study drug discontinuation, the fistula patency outcome assessment may be completed at any time within the 30 days following study drug discontinuation.

7. SECONDARY OUTCOME MEASURES

7.1 Fistula Suitability for Dialysis

Suitability for dialysis is defined as the ability to use the fistula for dialysis for at least 4 weeks and obtain a minimal nominal dialysis blood flow of 300 ml/min. To meet the 300 ml/min dialysis blood flow criterion all blood flow measurements recorded after the first hour and before the last 15 minutes of the dialysis session must be ≥300 ml/min. In order to distinguish fistula inadequacy from poor dialysis needle placement which might occasionally occur and result in low blood flow, the requirement for nominal blood flow of ≥300 ml/min must be met during at least 8 dialysis treatments during the 12-session ascertainment period. Fistulae suitable for dialysis will include those modified radiologically or surgically. Radiological modification may include percutaneous balloon angioplasty of stenoses, or pharmacological or mechanical thrombolysis. Surgical modification may include thrombectomy, or revision of the arteriovenous anastomosis as long as the same artery and vein are used.

The fistula suitability outcome ascertainment will begin 120 days after creation of the fistula for patients on dialysis prior to creation of the fistula. For patients who have not initiated dialysis at the time of fistula creation, fistula suitability ascertainment will begin 120 days after fistula

creation if dialysis is initiated within 4 months of fistula creation, or at the onset of initiation of dialysis if dialysis is initiated more than 4 months after fistula creation. The fistula will be considered suitable if the machine blood flow requirements are met for 8 of 12 consecutive dialysis sessions that take place. The first of these 12 sessions must occur between 120 and 150 days after fistula creation. For patients who initiate dialysis >120 days after fistula creation the suitability ascertainment period will begin with the first dialysis session and will end with the 12th consecutive dialysis session that takes place, or by 60 days after initiation of dialysis, whichever comes earlier.

Initial unsuccessful use of the fistula will not preclude attainment of the fistula suitability outcome as long as suitability criteria are met during the ascertainment periods described above.

7.2 Fistula suitability for dialysis without radiological or surgical modification

Suitability for dialysis criteria is defined as in Section 7.1 except that the fistula cannot be modified radiologically or surgically. Modified fistulae will be considered to have failed on the date of modification.

8. STATISTICAL DESIGN

8.1 Sample Size Calculations

From review of the literature, it is estimated that fistula thrombosis at 6 weeks (primary outcome) will occur in 25% of patients treated with placebo and failure to achieve fistula suitability for dialysis (secondary outcome) will occur in 40% of patients treated with placebo[14, 28-35, 48]. In order to detect a 30% reduction in fistula thrombosis rate with 85% power and a 2 sided-alpha level of 0.05, 1284 patients are required (642 in each treatment group) assuming a 5% loss to follow-up rate, a 3% treatment drop-in rate, and a 3% treatment drop-out rate. This sample size also includes a slight (2.7%) upward adjustment to account for the O'Brien-Fleming stopping rule suggested by the Steering Committee. Under a fixed sample size design, the sample size of 1,284 would provide approximately 80% power to detect a 20% reduction in failure to achieve fistula suitability for dialysis.

Addendum: As of June 1, 2004 the recruitment period of the study was extended from 48 to 51 months based on the recommendation of the Data Safety and Monitoring Board (External Advisory Committee).

8.2 Data Analysis

8.2.1 Interim Monitoring and Analysis

The External Advisory Committee will monitor the safety of the patients during the course of the study and evaluate interim analyses of efficacy performed by the Data Coordinating Center. The Steering Committee recommends that the External Advisory Committee consider a formal statistical stopping guideline based on a spending function with an O'Brien-Fleming boundary based on 5 annual looks at the data, including 4 interim and 1 final analysis.

8.2.2 Final Analysis

8.2.2.1 Baseline Comparability

To assess external generalizability, 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 randomized treatment groups to identify any imbalances.

8.2.2.2 Outcome Measures

Primary Analysis of Fistula Patency at 6 Weeks

The primary analysis will evaluate the effect of randomization to clopidogrel vs. placebo on the probability that a new fistula will be patent six weeks after randomization. This analysis will be carried out by applying the Mantel-Haenszel test to compare the proportion of patent fistulas at six weeks with stratification for Clinical Center and the location of the fistula. The comparison of the clopidogrel 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.

Analyses of Secondary Outcomes

The Mantel-Haenszel test (with stratification for Clinical Center and fistula location) will also be used to evaluate the effect of randomization to clopidogrel on the two main secondary outcomes:

a. the proportion of fistulae suitable for dialysis with or without radiological or surgical modification in the two treatment groups (secondary outcome measure).
b. the proportion of fistulae suitable for dialysis without radiological or surgical modification in the two treatment groups (secondary outcome measure).

Other Secondary Analyses

Secondary analyses will include an analysis of the three outcome measures for patients in whom study drug is not deliberately discontinued during the six week study drug administration period. Study outcomes will also be analyzed using logistic regression and adjusting for additional covariates found by interactive data analysis to be predictive of the primary or secondary outcomes. Death rates in active drug and placebo groups will also be compared.

8.3 Data Quality Control at the Data Coordinating Center

The DCC will regularly provide feedback on measures of the quality of its own performance, including rates of computer down time, rates of randomization of ineligible patients, and time it takes for the DCC to make corrections to the database once a clinical center has responded to a data discrepancy inquiry.

9. 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 (clopidogrel or placebo) is shown to be superior at an interim analysis based on the statistical stopping guideline (Section 8.2.1). 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 are 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.

10. REGULATORY CONSIDERATIONS

10.1 Institutional Review Boards (IRBs)

The protocol will be submitted to the IRB of each Clinical Center for review and approval. 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.

10.2 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.

11. PILOT STUDY

Prior to conducting the full-scale trial detailed in Sections 1-10, a pilot study will be performed to evaluate the feasibility of performing the full-scale trial. Because the Clinical Centers are comprised of multiple and geographically disparate sites, and because many of the patients eligible for enrollment in the study will not yet be on chronic dialysis, one of the most challenging aspects of the full-scale trial will be identification of eligible patients. An additional challenge will be to perform both randomization to treatment arm and study drug delivery within the time constraints of the full-scale trial protocol. Thus, the pilot study is designed to evaluate the following specific logistical issues:

1. Ability of centers to identify and enroll patients
2. Ability of centers to randomize and provide study drug to enrolled patients within one calendar day following fistula creation surgery

11.1 Pilot Study Design and Overview

The pilot study is an open-label trial in which patients scheduled to undergo creation of a new upper extremity native fistula will be randomized to receive clopidogrel or no study drug for six weeks following fistula creation surgery. Randomization will be on a 7:3 active drug: no drug allocation, and will be stratified by Clinical Center. The sample size is 50 patients (10 patients per Clinical Center) to be enrolled over a nine week period. For patients randomized to the clopidogrel arm, study drug administration will begin within one calendar day following native AV fistula creation and continue for six weeks following surgery. Fistula patency will be evaluated by physical examination six weeks after fistula creation. Participation in the pilot study will end at the 30-day follow-up telephone call to the patient following the six-week evaluation. The study outcomes include: number of patients enrolled by each Clinical Center during the nine week enrollment period, distribution of patient enrollment from the multiple sites comprising each Clinical Center, proportion of enrolled patients that are randomized within one calendar day following fistula creation surgery, proportion of patients randomized to clopidogrel that receive drug supply within one calendar day following fistula creation surgery, and proportion of patients in the clopidogrel arm who remain on the study drug for the entire six-week drug administration period.

11.2 Pilot Study Enrollment and Randomization

Patients will be recruited from the hemodialysis and chronic renal failure populations of the participating Clinical Centers. The goal of each Clinical Center will be to enroll a total of ten patients. Each Clinical Center should enroll patients from as many of the individual sites comprising the Clinical Center as possible. No more than five patients should be enrolled from the "main" site (i.e., the site of the Clinical Center's principal investigator), and at least one patient should be enrolled from any site at which anticipated enrollment in the full-scale trial is twenty patients or greater. Identification of potential study participants and the informed consent process will occur as outlined for the full-scale trial (see Section 3).

11.2.1 Pilot Study Eligibility Criteria

Inclusion and exclusion criteria are listed below. Eligibility criteria are the same as for the full-scale trial (see Section 3.1) except that in the pilot study patients do not need to have an anticipated start of hemodialysis within six months of enrollment or be expected to stay at a participating dialysis facility for at least six months.

Inclusion Criteria

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. Planned creation of native upper extremity AV fistula.
4. The patient is not on aspirin, or the patient is on aspirin but has not had a myocardial infarction or a cerebrovascular accident within the past 12 months.
5. The patient's physician(s) will allow the patient to participate.
6. Ability to give informed consent.

Exclusion Criteria

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 with proton pump inhibitors, H2 blockers or therapy for Helicobacter pylori within three months prior to obtaining consent.
6. A condition which prohibits discontinuation of anticoagulant drugs, aspirin, nonsteroidal anti-inflammatory drugs, or glucocorticoids during the six week study drug administration period. Use of heparin during dialysis is allowed.
7. Current unstable angina.
8. Required use of clopidogrel.
9. Known hypersensitivity to clopidogrel.
10. Medical considerations making anti-platelet therapy dangerous.
11. Current uncontrolled hypertension with systolic blood pressure in excess of 200 mm Hg or diastolic blood pressure in excess of 115 mm Hg at the time of enrollment.
12. Baseline platelet count less than $75{,}000/mm^3$.
13. Prolonged prothrombin time (INR >1.5) or partial thromboplastin time (5 or more seconds above upper limit of normal).
14. Known advanced liver disease with decompensated cirrhosis, jaundice, ascites or bleeding varices.
15. Current problem with substance abuse.
16. Concurrent participation in another medical intervention trial.
17. Anticipated non-compliance with medical care based on physician judgment.
18. Patient refusal.

11.2.2 Pilot Study Randomization

As in the full-scale trial, randomization will be performed post-operatively via the Internet using a web browser following verification of eligibility by the Data Coordinating Center. Patients will be randomized to clopidogrel or no drug at a 7:3 ratio with stratification by Clinical Center. Randomization is unbalanced in favor of clopidogrel in order to increase the ability to evaluate 1) the procedure for delivering study drug to patients within the allotted time period following fistula creation surgery, and 2) drug tolerability. Stratification by Clinical Center will allow the study personnel at each Clinical Center to evaluate their ability to deliver study drug to seven of their ten enrolled patients.

11.3 Pilot Study Visits and Patient Contacts

Patients will be evaluated at two study visits. See Section 11.9 for details regarding the data collected at each visit. The first study visit will be a screening evaluation during which eligibility will be assessed, informed consent and baseline demographic/laboratory data will be obtained, and the quality of life questionnaire will be performed (same procedures as for full-scale trial). As in the full-scale trial it is preferred that this visit occur prior to creation of the new native fistula; however, enrollment will be permitted up to one calendar day following fistula creation. Randomization for treatment assignment will be performed following fistula creation surgery after verification that a fistula was created. Randomization and study drug delivery to the patient must occur such that study drug administration can begin within one calendar day following fistula creation surgery. For patients randomized to clopidogrel, study drug will be delivered to the patient within one calendar day following fistula creation surgery and instructions to begin the study drug will be given by study personnel either in person or by telephone. During this contact, the study coordinator or investigator will ensure that the patient knows how to contact study personnel if questions arise or adverse events occur. Patients randomized to no drug will be informed of this by study personnel either in person or by telephone. If a patient is not randomized because of failure to create a native fistula, the patient will be informed that he/she will not be participating in the study.

The second study visit will occur six weeks after fistula creation (coinciding with completion of study drug for those patients randomized to clopidogrel). At this visit the patency of the fistula will be determined by physical examination (i.e., presence of thrill and bruit). Adverse events and side effects of treatment will be reviewed. Study drug pill count will be performed. A quality of life questionnaire will be completed. Study personnel will contact patients by telephone 30 days after the six-week evaluation to identify any adverse events that occurred after the six-week visit. Participation in the trial will end with this telephone call.

11.4 Study Drug Administration in Pilot Study

Patients randomized to clopidogrel will be given a six-week supply of clopidogrel 75 mg tablets and instructed to take one tablet by mouth each day starting within one calendar day following fistula creation surgery for six weeks. Patients randomized to no drug will not receive any study medication.

11.5 Initiation of Fistula Use in Pilot Study

As in the full-scale trial, decisions about when to initiate use of the new fistula will be left to the patient's nephrologist and/or vascular surgeon.

11.6 Intercurrent Events and Interruptions in Treatment in Pilot Study

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. For all patients bleeding events and surgery or other invasive procedures will be handled as in the full-scale trial (see Sections 4.4.1 – 4.4.3). Indications for discontinuation of clopidogrel will be the same as the events leading to study drug discontinuation in the full-scale trial (see Section 4.4.4).

11.7 Concomitant Medications in the Pilot Study

Patients should not receive any other antiplatelet or antithrombotic agents other than intra-dialytic heparin during the six weeks following fistula creation. Specifically, aspirin, non-steroidal anti-inflammatory drugs, dipyridamole, sulfinpyrazone, and warfarin are not to be used. Acetaminophen, codeine, or other analgesics not containing aspirin or NSAIDs may be used for

pain. If the proscribed agents are required (e.g., warfarin for deep venous thrombosis or atrial fibrillation, aspirin for new cardiovascular event) during the period of study drug administration, study medication should be discontinued and the patient should continue to be followed. For patients on aspirin prior to enrollment, the aspirin should be discontinued seven days prior to fistula creation surgery and resumed after the six week study drug administration period.

11.8 Events Leading to Withdrawal from the Pilot Study

A patient will be withdrawn from the pilot study for the following reasons:
1. Follow-up during the study period is not possible because the patient moves to a distant location.
2. The patient is judged lost to follow-up after repeated attempts to contact have failed.
3. Withdrawal of consent.
4. Death.

11.9 Duration of Participation in Pilot Study

Participation in the pilot study will end at the 30-day follow-up telephone call to the patient following the six-week study visit.

11.10 Pilot Study Data Collection

Baseline data collection will be identical to that of the full-scale trial (see Section 5.1). As in the full-scale trial, eligibility criteria and baseline laboratory data must be obtained no more than 30 days prior to randomization. Data collected at the six-week visit will be identical to that of the full-scale trial (see Section 5.2).

11.11 Pilot Study Outcomes

The purpose of the pilot study is to evaluate specific logistical issues of the full-scale trial. In particular, the ability of each Clinical Center to identify eligible patients from the multiple sites comprising the Clinical Center and to randomize patients and deliver study drug within the time constraints dictated by the full-scale protocol will be evaluated. The following outcomes will be ascertained:
1. Number of patients enrolled by each Clinical Center during the nine-week enrollment period.
2. Distribution of patient enrollment from the multiple sites comprising each Clinical Center.
3. Proportion of enrolled patients that are randomized within one calendar day following fistula creation surgery (overall and within Clinical Centers).
4. Proportion of patients within the clopidogrel arm that receive the drug supply within one calendar day following fistula creation surgery (overall and within Clinical Centers).
5. Proportion of patients in the clopidogrel arm that remain on the study drug for the entire six-week drug administration period.

11.12 Pilot Study Data Analysis

Analyses to be performed for the full-scale study will be done on the pilot trial data, but the sample size will not be sufficient to answer the questions of the full-scale trial with adequate power.

We will evaluate the rate at which potential patients are identified to determine if the speed is sufficient to proceed with full-scale trial enrollment. We will evaluate reasons patients are not eligible to determine if eligibility criteria need to be changed for the full-scale trial. We will evaluate reasons eligible patients are not randomized to determine if the randomization procedure needs to be changed for the full-scale trial. We will evaluate the proportion of patients who begin taking drug by the end of the calendar day after surgery (overall and by Clinical Center) to determine if we have adequate plans for delivering drug to the patients in the full-scale

trial. We will evaluate medication compliance to determine if our plans for promoting compliance are sufficient for the full-scale trial.

11.13 Pilot Study Safety Monitoring

The External Advisory Committee (EAC) for the full-scale trial will also serve to review the accumulating data of the pilot study with regard to safety (see Section 9). Reports of the EAC will be submitted to all IRBs involved in the trial. Adverse event reporting will be performed as in the full-scale study (see Section 9).

11.14 Pilot Study Regulatory Issues and Quality Control

The pilot study protocol will be submitted to the IRB of each Clinical Center for review and approval. 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.

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. Clinically relevant information obtained as a result of participation in this trial may be placed in the patient's medical record as progress notes.

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