# Effect of Warfarin Anticoagulation on Below-Knee Polytetrafluoroethylene Graft Patency

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When polytrafluoroethylene (PTFE) must be used for below-knee bypass to achieve limb salvage, effective anticoagulation with warfarin may improve graft survival. We analyzed our practice of routinely using oral anticoagulation to improve graft patency rates for PTFE grafts to below-knee popliteal and crural vessels in limb salvage procedures. We reviewed our established vascular database from February 1999 through April 2003 to identify those patients who required below-knee and tibial artery bypass with PTFE for critical limb ischemia. All patients were initiated on warfarin anticoagulation postoperatively, with an international normalized ratio (INR) of 2.0-3.0 considered therapeutic. All patients were discharged in the therapeutic range. Life-table analysis and Kaplan-Meier estimates were used to compare primary patency rates with regard to INR and position of distal anastomosis. Cox proportional hazards analysis was performed to compare the patency rates for grafts with therapeutic versus subtherapeutic anticoagulation while correcting for variability in distal runoff. Between February 1999 and April 2003, 74 patients (mean age, 69.2 years; 58% men) had 77 below-knee PTFE bypasses. Indications for operation included rest pain (43), ischemic ulcer (27), and gangrene (7). Patients presenting with occluded grafts more often had a subtherapeutic INR. Patients with a subtherapeutic INR (≤1.9) had a median primary graft patency of 6.8 months and those with a therapeutic INR (≥2.0) had a median primary graft patency of 29.9 months ($p = 0.0007$). Analysis by Cox proportional hazards model demonstrated a significantly better graft patency rate in patients with a therapeutic INR regardless of outflow vessel. The patency rates of PTFE grafts to infrageniculate vessels may be improved by effective anticoagulation with warfarin. This improved patency rate may also result in improved limb salvage and further support the use of PTFE grafts for critical limb ischemia when autogenous vein is not available. Predictably, the best results are seen with an INR therapeutic range of 2.0 to 3.0.

## INTRODUCTION

Lower extremity peripheral arterial disease is common, affecting 20-30% of our aging population.[1] When patient symptoms progress to a level consistent with critical limb ischemia, limb salvage versus primary amputation must be considered. Studies have shown that revascularization is cost-effective compared to primary amputation.[2] Additionally, limb salvage improves quality of life and maintains functional status for most patients with lower extremity bypass. Greater saphenous vein (GSV) has been demonstrated to be the conduit of choice for infrainguinal bypass, with cumulative patency and limb salvage rates exceeding 80% at 5 years.[3] The need for distal arterial reconstruction in the absence of suitable autologous conduit is becoming a much more frequently observed scenario. When GSV is unavailable, alternate conduit vein grafts have been created with acceptable results.[4] Still, vascular surgeons frequently encounter patients in which no suitable vein is available and limb salvage procedures must be performed with prosthetic bypass grafts.

When peripheral arterial reconstruction is undertaken with prosthetic conduit, various technical, adjunctive measures can be applied to en-

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hance graft patency. Technical adjuncts such as arteriovenous fistulas (AVF) and vein cuffs have been shown to improve distal anastomotic flow dynamics, thereby increasing cumulative patency rates for prosthetic bypass grafts.[5-9] All patients included in the present study underwent bypass with a distally cuffed polytetrafluoroethylene (PTFE) conduit (Distaflo, Impra; Tempe, AZ). These grafts are engineered to create flow dynamics similar to those of a vein cuff at the distal anastomosis. We believe anticoagulation with warfarin (Coumadin) is also an effective adjunct to bypass with prosthetic conduit, and we routinely use warfarin anticoagulation when below-knee and tibial artery PTFE bypass is performed.

The current study addresses the effect of routine postoperative warfarin on the primary patency of lower extremity bypass grafts created with prosthetic graft material. More specifically, we hope to identify the most appropriate use for warfarin anticoagulation in the setting of prosthetic lower extremity bypass grafting.

## METHODS

Candidates for inclusion in this study were identified by review of an established, computerized vascular surgery database. All patients undergoing distal (below-knee popliteal, tibial, or pedal artery) arterial reconstruction with prosthetic graft material were considered eligible. Between February 1999 and April 2003, 77 below-knee prosthetic grafts were created in 74 patients to treat critical limb ischemia. All operations were performed at either the University of Alabama (UAB) Hospital or the Birmingham Veteran's Administration (VA) Hospital in Birmingham, AL. Preoperative arterial assessment was performed with digital subtraction angiography to evaluate arterial anatomy. B-mode ultrasound evaluation was additionally performed to identify and characterize all available autogenous vein. Patients were considered for reconstruction with artificial conduit if no suitable vein or an insufficient amount of suitable vein was identified by ultrasound examination. The decision to proceed with prosthetic graft construction was made by the surgeon of record upon review of all preoperative angiographic and ultrasound data. All patients received postoperative anticoagulation with intravenous heparin. Heparin anticoagulation was subsequently converted to adjusted-dose warfarin with a target international normalized ratio (INR) range of 2.0-3.0.

Postoperative follow-up consisted of routine visits for wound examination and confirmation of graft patency. Patients were seen initially at 1 to 3 weeks for routine postoperative examination. Postoperative graft surveillance with duplex ultrasound was performed according to our usual lower extremity bypass graft surveillance protocol: grafts are examined within the first 6 weeks following operation, and subsequent exams are performed every 3 months for 1 year, every 6 months for 1 year, then once yearly for the lifetime of the graft. If flow abnormalities or graft occlusions were identified, angiography was performed as deemed necessary by the surgeon of record. Patient data regarding intraluminal graft flow velocities, graft patency, and coagulation studies were maintained in a computerized database for future reference.

All patients had INR values documented in the therapeutic range at the time of discharge. Outpatient management of anticoagulation (adjustment of Coumadin dose based on INR value) was performed by the patient's primary physician in >90% of cases. These patients had warfarin dose adjustments based on the protocol of their treating physician. A physician-supervised (nonsurgical), UAB-affiliated Coumadin clinic was available to manage those who preferred or required this arrangement. Patients treated in the VA system were managed by their primary VA physician.

The protocol for INR-based warfarin dose adjustment in the UAB-affiliated Coumadin clinic is as follows. INR values are recorded within 1 week of discharge from the hospital. Values are then monitored on a weekly basis until three consecutive INR measurements are recorded within the desired therapeutic range. Following the three consecutive desired measurements, patients are monitored bimonthly for 1 month, then monthly, provided that desired INR values are maintained. If INR values become sporadic or fall after establishment of a consistent dose of warfarin, the frequency of INR measurements is changed at the direction of the physician supervising the clinic. Anticoagulation data were obtained from either the monitoring physician's records or from our Coumadin Clinic registry at the time of follow-up in the vascular clinic.

Coagulation data, specifically INR values, were used to stratify both patent and failed grafts. Grafts that remained primarily patent were categorized according to the INR value recorded at the time of most recent duplex ultrasound documentation of graft patency. In the case of failed grafts, the INR value at presentation with graft thrombosis was recorded. Three groups were ultimately developed to compare patency on the basis of level of anticoagulation as measured by INR. In our initial anal-

**Table I.** Medical comorbidities observed in study patients

| Medical condition | Patients (*n*) | % of total (*n* = 74) |
|---|---|---|
| Coronary artery disease | 51 | 68.9% |
| Coronary artery bypass grafting | 32 | 43.2% |
| Hypertension | 50 | 67.56% |
| End-stage renal disease (or chronic renal insufficiency) | 13 | 17.56% |
| Diabetes mellitus | 38 | 51.35% |
| Congestive heart failure | 16 | 21.62% |
| Atrial fibrillation | 5 | 6.76% |
| Hyperlipidemia | 9 | 12.16% |
| Prior myocardial infarction | 12 | 16.21% |

ysis, an INR ≥2.0 was designated as therapeutic or the minimum desired level of anticoagulation. INR values ≤1.9 were initially considered to be subtherapeutic. A significant difference in patency was observed between these two groups. In an attempt to further investigate the effect of INR on graft patency, a second analysis was performed using three INR groups for stratification. This analysis compared therapeutic (INR ≥ 2.0), intermediate (INR = 1.5-1.9), and subtherapeutic (INR < 1.5) grafts.

Median primary graft patency for each group was determined by Kaplan-Meier analysis. The log-rank test was used to test for differences between the coagulation groups. Proportional hazards regression was used to account for influence of outflow vessel in addition to level of anticoagulation. Chi-squared tests were used to assess the risk of graft failure by degree of anticoagulation (measured by INR). All statistical analyses were performed using SAS version 9.00 (SAS Institute Inc., Cary, NC).

## RESULTS

Between February 1999 and April 2003, 74 patients underwent 77 lower extremity bypasses to infrageniculate arteries with prosthetic graft material. All grafts were constructed using distally cuffed PTFE grafts. Distal arteriovenous fistulas (dAVF) were additionally created in six grafts. With the exception of these six grafts, no further technical adjuncts were applied. Forty-three patients were male (58.1%) and the mean age was 69.2 (range, 38-87) years. Patients in the study group demonstrated the usual spectrum of vascular risk factors and comorbidities encountered in the practice of vascular surgery (Table I).

There were five perioperative deaths, yielding a 6.4% perioperative mortality rate. One death was related to myocardial infarction and subsequent multisystem organ failure. An additional cardiac death occurred secondary to irreversible, sustained ventricular tachycardia. The remaining deaths were respectively related to respiratory failure, complications of HIV infection, and hypercoagulable state, and one was from undetermined causes. Nine (10.5%) acute (within < 30 days) graft occlusions were identified, six of which resulted in major amputation. Six of the nine acute occlusions occurred in the immediate postoperative setting (7.1%).

**Table II.** Vessel used as inflow site for distal PTFE bypass grafts

| Inflow vessel | *n* (%) |
|---|---|
| Common femoral | 59 (76.6) |
| Graft | 6 (7.8) |
| Superficial femoral | 9 (11.7) |
| Profunda | 2 (2.6) |
| Popliteal | 1 (1.3) |
| | *n* = 77 |

Indications for operation included rest pain in 43 cases (55.8%), nonhealing ulceration in 27 (35.1%), and gangrene in 7 (9.0%). The most common inflow vessel used was the common femoral artery (76.6%) (Table II). The most common outflow vessel used was the posterior tibial artery (36.4%) (Table III).

Preliminary data analysis compared grafts designated therapeutic (INR ≥ 2.0, n = 37) with those designated subtherapeutic (INR ≤ 1.9, *n* = 40). Comparison of primary graft patency between these two groups by means of Kaplan-Meier estimates revealed superior primary patency in the therapeutic group with a median primary patency of ≥29.9 months (standard error [SE] = 2.23) vs. 6.8 months (SE = 2.34) ($p = 0.0007$) (Fig. 1). It should be noted that the median primary patency for the therapeutic group is in actuality an estimate secondary to the fact that >50% of the grafts within

**Table III.** Target vessel used as outflow for distal PTFE bypass grafts

| Outflow vessel | *n* (%) |
|---|---|
| Posterior tibial | 28 (36.4) |
| Peroneal | 26 (33.7) |
| Anterior tibial | 10 (12.9) |
| Below-knee popliteal | 8 (10.4) |
| Tibioperoneal trunk | 3 (3.9) |
| Dorsalis pedis | 2 (2.6) |
| | *n* = 77 |

this group were still primarily patent at the end of the maximum follow-up period of 29.9 months.

Supplemental analysis with grafts grouped according to more strict stratification of INR values yielded similar results. Among the three specific groups, the therapeutic group again demonstrated superior primary patency (median, 29.9 months; SE = 2.23). Grafts in patients with INR values in the intermediate group had a median primary patency of 9.2 months (SE = 4.38), with the subtherapeutic group exhibiting a median primary patency of 5.3 months (SE = 0.99) ($p = 0.0001$) (Fig. 2).

Wide variation in graft survival with respect to distal outflow vessel was identified during preliminary analysis. The anterior tibial group had the shortest survival time (median, 3.8 months), with peroneal grafts having the longest survival (median, 26.2 months). Overall differences were not found to be statistically significant. To more specifically determine the relationship of outflow vessel to primary graft patency, Cox proportional hazard analysis was used to determine if the level of anticoagulation with warfarin would prove to be the only source of variation. This analysis revealed that grafts in the therapeutic group, and to a lesser degree those in the intermediate group, had a significantly lower hazard of failure than that of grafts in the subtherapeutic group, even while accounting for the influence of outflow vessel.

Risk of graft failure by level of anticoagulation (INR) was determined using chi-squared analysis. Comparison between therapeutic and subtherapeutic groups demonstrated a reduced failure risk among grafts in the therapeutic group, 18.92% vs. 60% (chi-squared test, $p = 0.0002$) (Fig. 3). Similar comparison following further division of the grafts also demonstrated reduced failure risk among therapeutic grafts, with 18.92% vs. 46.67% for intermediate and 68% for subtherapeutic grafts (chi-squared test, $p = 0.0005$) (Fig. 4).

During the course of the study, we observed five major bleeding episodes (6%, or 1.45% per year), which compares favorably with other studies on warfarin-related bleeding complications.[10-13] A significant bleeding event was characterized by bleeding that required transfusion, hospitalization, or cessation of anticoagulation. One of the bleeding episodes proved to be a fatal intracranial hemorrhage that occurred during a patient fall 3.5 years following operation. Interestingly, this was the only patient whose INR (1.9) was not abnormally elevated at the time of the bleeding incident. Because of the patient's advanced age and debilitated state, the family elected not to pursue intervention and the patient expired.

There were three patients included in the present study who experienced gastrointestinal (GI) hemorrhage (two upper and one lower) while taking warfarin. All three patients were found to have INR levels well above the desired therapeutic range (2.0-3.0) when the bleeding incident was identified. One patient experienced upper GI bleeding (INR 5.3) requiring transfusion of packed red blood cells and fresh frozen plasma. This patient was found to have bleeding esophageal varices and Coumadin was subsequently discontinued. The second upper GI bleed occurred in a patient with INR > 12.0. The patient was pharmacologically reversed with aquamephyton (vitamin K) and fresh frozen plasma transfusion, which resulted in cessation of bleeding. This patient was eventually released from the hospital on warfarin with close follow-up and no further bleeding events identified. The third patient had hematochezia related to diverticulosis and an INR of 3.7. This patient was successfully managed conservatively, without transfusion, by discontinuing warfarin anticoagulation. Aspirin and Plavix were subsequently used in the place of warfarin.

The final bleeding complication in the series was wound related. This patient was noted to develop a wound hematoma on postoperative day 10 (INR 3.6) that required operative evacuation. This patient was reinitiated on warfarin therapy without further bleeding complications.

## DISCUSSION

Peripheral arterial bypass for critical limb ischemia in the absence of autogenous conduit is a challenging problem that seems to be confronting vascular surgeons with increasing frequency. Primary amputation continues to be an unsavory option for patients and surgeons alike. Compared to primary amputation, revascularization has been proven to be cost-effective and improve the quality of life and functional status of patients.[2,14]

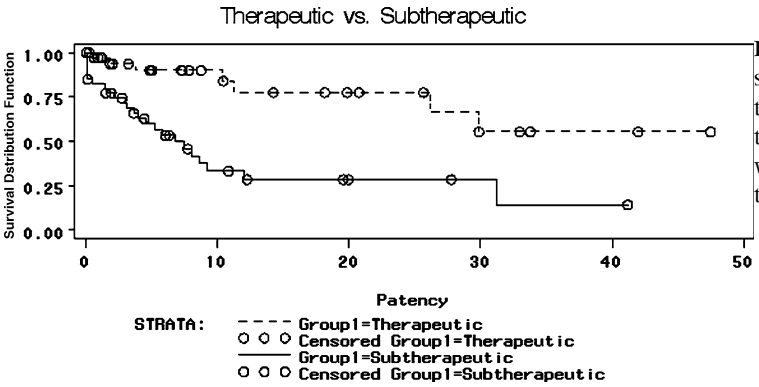


**Fig. 1.** Survival function for therapeutic versus subtherapeutic groups. There were 77 observations. Kaplan-Meier estimate of median survival time for the therapeutic group (half not failed) was 29.9 months (SE = 2.23) and for the subtherapeutic group was 6.8 months (SE = 2.34).

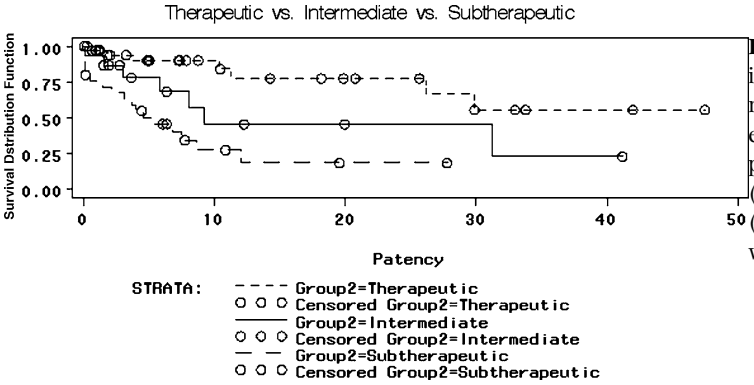


**Fig. 2.** Survival function of therapeutic versus intermediate versus subtherapeutic groups. The number of observations was 77. Kaplan-Meier estimate of median survival time for the therapeutic group (half not failed) was 29.9 months (SE = 2.23), for the intermediate group was 9.2 (SE = 4.38), and for the subtherapeutic group was 5.3 (SE = 0.99).

It has been extensively documented that the patency rates for autologous distal bypass grafts are superior to those for prosthetic lower extremity bypass grafts,[3,15-17] particularly for bypasses to crural vessels. However, certain studies have demonstrated acceptable patency results for bypass grafts constructed with PTFE grafts. In a randomized trial of patients undergoing peripheral bypass, Veith et al.[16] demonstrated a 76% 4-year patency rate with saphenous vein graft compared to 54% with PTFE. Kram et al.[18] produced acceptable patency and limb salvage rates with PTFE grafts to popliteal vessels, even in the setting of poor outflow.

Technical adjuncts such as creation of dAVF or of vein cuffs at the distal anastomosis have been shown to favorably influence long-term prosthetic bypass graft patency. In the instance of dAVF, the enhanced patency is thought to be related to accelerated flow through the distal anastomosis as a result of communication with low-resistance venous circulation. Kallakuri et al. demonstrated a five times greater flow rate in tibial bypass grafts with the addition of dAVF[5] Another study using alternative conduit (glutaraldehyde-tanned human umbilical cord vein graft) to crural vessels showed improved patency rates when dAVF were used.[19] Anastomotic vein cuffs have also been shown to improve the anastomotic flow dynamics by reducing turbulence and improving compliance of the graft-native vessel interface. Numerous studies have demonstrated improved patency rates when a vein cuff is added to the distal anastomosis in below-knee PTFE bypass grafts.[6-9]

The use of anticoagulation as a postsurgical adjunct to enhance prosthetic bypass graft patency and performance has also been previously described. The use of warfarin anticoagulation in one study was specifically associated with a significant reduction in bypass graft failure (femoral-popliteal reversed saphenous vein) compared to controls.[20] More importantly, a randomized clinical trial in patients at high risk for graft failure (poor runoff, marginal quality vein, or previously failed bypass) yielded a 78% vs. 41% 3-year primary patency rate with postoperative warfarin use.[21] Limb salvage rates were also shown to be significantly higher in this group in which 90% of bypasses were to the tibial arteries. Many of the patients included in the present analysis are at increased risk for graft failure, whether related to previous failed bypass grafts, suboptimal outflow,

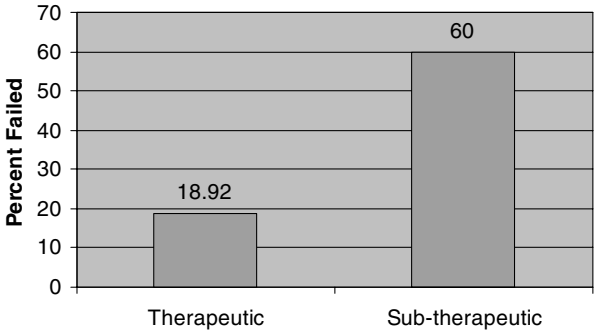


**Fig. 3.** Graft failure risk based on INR (therapeutic and subtherapeutic). $p = 0.0002$.

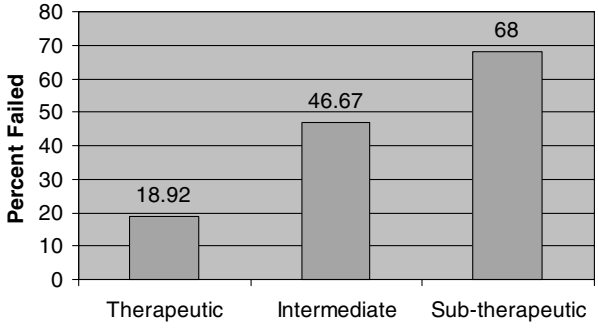


**Fig. 4.** Graft failure risk based on INR (therapeutic, intermediate, and subtherapeutic). $p = 0.0005$.

or limited autologous conduit. None of the patients in the present analysis had sufficient autologous conduit for autogenous bypass graft construction. We feel that this patient population will benefit most from routine postoperative warfarin anticoagulation.

In addition to improving graft performance and limb salvage, long-term warfarin has been shown to improve overall patient survival in those patients requiring femoral-popliteal revascularization,[22] an effect that may be linked to protection against thrombotic occlusion of the coronary circulation in study patients. Considering the overall medical profile (particularly as it relates to coronary artery disease) of patients requiring lower extremity bypass for limb salvage, this could prove to represent an additional, unexpected benefit associated with routine postoperative warfarin use. Further study will be required to confirm or refute this suggestion.

We believe our data support the use of warfarin as an antithrombotic adjunct to distal revascularization with prosthetic grafts to improve primary graft patency. The present analysis suggests that superior primary patency rates are achieved when the INR is maintained at a level ≥2.0. We strive to keep INR values in our suggested therapeutic range of 2.0-3.0. Additionally, grafts in our intermediate group also appear to gain a slight advantage of increased primary patency (approximately 4 months) over that for subjects with subtherapeutic INR levels. We acknowledge that our analysis is limited by the retrospective nature of our review, limited long-term follow-up (though some grafts are being followed at up to 5 years), and relatively small sample size.

In summary, adjusted-dose warfarin (target INR, 2.0-3.0) significantly improves primary patency for infrageniculate PTFE bypass grafts. We advocate warfarin anticoagulation for all patients undergoing below-knee revascularization with PTFE (in the absence of contraindications). Additionally, we continue to advocate revascularization with prosthetic material over primary amputation.

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