Low-Intensity Warfarin Is Ineffective for the Prevention of PTFE Graft Failure in Patients on Hemodialysis: A Randomized Controlled Trial

MARK A. CROWTHER,* CATHERINE M. CLASE,* PETER J. MARGETTS,* JIM JULIAN,† KIM LAMBERT,* DENISE SNEATH,‡ RYUTA NAGAI,‡ SARAH WILSON,* and ALISTAIR J. INGRAM*

*Department of Medicine and † Department of Epidemiology and Biostatistics, McMaster University, Hamilton, Ontario, Canada; and ‡ Division of Nephrology, Hotel Dieu Hospital, St. Catharine’s, Ontario, Canada

Abstract. Polytetrafluoroethylene (PTFE) dialysis grafts in patients with end-stage renal disease (ESRD) are prone to thrombotic failure. The objective of this multicenter, randomized, double-blind, placebo-controlled clinical trial was to determine if warfarin reduces the risk of failure of PTFE dialysis grafts. Patients with ESRD and newly placed PTFE grafts were studied at community and academic dialysis centers in Southwestern Ontario. Patients were allocated to receive warfarin or matching placebo, with the warfarin administered to achieve a target INR of 1.4 to 1.9. Time to graft failure was the main outcome measure. A total of 107 patients (56 allocated to warfarin) were randomized. The time-to-event analysis revealed no significant difference in the likelihood of graft survival between the two groups (odds ratio, 1.76 in favor of placebo; 95% confidence interval, 0.72 to 4.34). Six major bleeds occurred in five patients allocated to warfarin compared with none in the patients who received placebo (P = 0.03). In conclusion, low-dose warfarin was associated with an excess of clinically important major bleeding in patients with ESRD enrolled in this study. Furthermore, low-intensity, monitored-dose warfarin does not appear to prolong PTFE graft survival.

Access complications account for 30% of hemodialysis patient hospital admissions (1), and it has been estimated that 14% of total Medicare end-stage renal disease (ESRD) expenditures relate to the treatment of complications of vascular access (2). Mechanical malfunction of access due to thrombosis accounts for much of this morbidity and resource utilization; prevention and treatment of thrombosis is consequently of major clinical and economic importance. Given its effectiveness for the prevention of thrombosis in other clinical settings, warfarin was used extensively in the first years of dialysis in an effort to prevent thrombotic failure of external arteriovenous shunts. However, despite reducing the risk of thrombosis in Scribner shunts (3,4), use of warfarin fell into disfavor because very high rates of serious hemorrhage were reported (5).

Currently, most North American hemodialysis patients use a polytetrafluoroethylene (PTFE) graft as their primary blood access (6–8). These grafts are subject to a high rate of failure attributable to acute thrombosis. To reduce the risk of thrombotic failure, many nephrologists prescribe anticoagulants. To our knowledge, there are no randomized clinical trials to support this widespread clinical practice, particularly the use of warfarin, to prevent thrombotic complications in PTFE grafts. To address this knowledge gap, particularly to determine whether warfarin is effective for the prevention of PTFE graft thrombosis, we performed a randomized trial, allocating patients with newly placed PTFE hemodialysis access grafts to receive either warfarin administered to achieve an INR of 1.4 to 1.9 or matching placebo. The primary efficacy outcome was the time to thrombotic graft malfunction, and the primary safety outcome was the frequency of hemorrhage.

Materials and Methods

Study Subjects and Randomization

This study was a multicenter, randomized, double-blind, placebo-controlled trial in which patients with newly placed (incident) PTFE grafts for hemodialysis access were eligible to participate. Two university-based teaching hospitals and a community dialysis unit participated. Consentig patients meeting inclusion and exclusion criteria (Table 1) were allocated, using a concealed computer-generated randomization scheme, to receive warfarin or matching placebo in random permuted blocks of four (DuPont Pharma, Mississauga, Canada). Patients were stratified by clinical center, use of antiplatelet therapy at the time of randomization, and whether the graft was placed in a patient currently receiving hemodialysis or in anticipation of the need for dialysis.

Treatment and Follow-Up

Study drug was initiated within 7 d of surgery. INR monitoring was initiated on day 3 after starting study drug and was continued according to a predefined protocol. INR was determined using Thromborel...
Table 1. Inclusion and exclusion criteria for the trial

Inclusion criteria
1. hemodialysis dependency or planned hemodialysis in near end-stage renal disease (ESRD) patients.
2. newly placed polytetrafluoroethylene (PTFE) graft.

Exclusion criteria
1. recent major hemorrhage (within the previous 6 mo); defined as bleeding requiring transfusion, bleeding in a critical site (retroperitoneal or intracranial), bleeding associated with hypovolemia or requiring admission to hospital, or bleeding resulting in ≥20 g/L (2 g/dl) drop in the hemoglobin.
2. allergy to warfarin.
3. persistent thrombocytopenia (platelet count <50 × 10^9/L).
4. inability to take oral medications.
5. presently taking warfarin for another indication.
6. expectation of recovery of renal function or life expectancy less than 2 mo.
7. lack of informed consent or inability to give informed consent.

S (Dade-Behring, Mississauga, ON), with instrument-specific ISI values of 1.23 to 1.28. INR results were called to a central warfarin monitor who was aware of the treatment allocation of each patient but was not otherwise involved in the study. The monitor reported directly to the appropriate study nurse or investigator at each clinical center. For patients randomized to receive warfarin, the true INR value was relayed; whereas for patients randomized to receive placebo, the warfarin monitor reported instead a sham INR derived from a randomly generated patient-specific schedule. The sham INR values reflected normal responses of the INR to initiation of warfarin therapy at this intensity and were similar to those used in previous studies (9).

Dose adjustments were then made in response to the true or sham INR according to a prespecified algorithm, with a target INR of 1.4 to 1.9. Between study initiation and July 1999, an arbitrary upper limit of 4 mg/d warfarin was employed, with the dual objects of maximizing patient compliance by limiting the number of capsules to be taken and reducing the likelihood of unanticipated excessive prolongation of the INR. (Previous data had suggested that the average dose of warfarin required to produce an INR of 2.0 to 3.0 in patients with normal renal function was between 4.0 and 5.0 mg/d). Patients with INR values of less than 1.4 on a 4-mg dose were maintained on that dose. At the first blinded interim analysis in June 1999, we noted that some patients experienced major bleeding, or who declined to continue medication, stopped taking study medication but continued to be followed. Patients were followed until graft thrombosis occurred, the patient died, or the study was closed. Patients who developed a short-term indication for warfarin therapy (such as acute venous thrombosis) were not excluded from the analysis during the period of treatment with open-label warfarin. All patients experiencing minor hemorrhage were encouraged to resume study drug as soon as possible after their event; only in the case of major or life-threatening hemorrhage was study drug permanently discontinued.

Sample Size and Statistical Analyses

A priori, we assumed that rate of PTFE graft failure over 2 yr without warfarin was 50% (11). Previous reports suggested that low-dose warfarin reduced the risk of venous catheter failure by 75% at 90 d (12). Using a conservative estimate of a 50% risk reduction in the rate of graft thrombosis (i.e., 25% percent rate of failure in the warfarin arm compared with a 50% rate of failure in the usual therapy arm), we anticipated a requirement for 57 patients per arm to achieve a statistically significant result (two-tailed α of 0.05 and power of 0.8), assuming a binomial distribution. To reflect loss of patients who die with a functioning graft (approximately 17% per year), we predicted recruitment requirements at 82 patients per arm. Follow-up of individual patients was planned until 6 mo after the final patient was enrolled. Thus the maximum possible follow-up on the first patient enrolled, assuming graft failure did not occur, would have been about 3.5 yr, based on our anticipated rates of recruitment.

The primary efficacy analysis of the study was an intention-to-treat comparison of graft survival between patients allocated to warfarin and those allocated to placebo, accounting for baseline strata. The primary safety analysis was a comparison of bleeding rates between the two groups using Fisher’s exact test. Major bleeding was defined as bleeding requiring transfusion, bleeding in a critical site (retroperitoneal or intracranial), bleeding associated with hypovolemia or requiring admission to hospital, or bleeding resulting in greater than a 20 g/L (2 g/dl) drop in hemoglobin. All other reported bleeding was recorded as minor bleeding. Asymptomatic decreases in the hemoglobin, often attributable to changes in erythropoietin dose were recorded but not counted as minor hemorrhage. Secondary (exploratory) analyses included an on-treatment analysis and a comparison of the likelihood of graft survival between patients who were or were not receiving antiplatelet therapy at the time of randomization. An interim analysis of safety and efficacy, blinded to the clinical investigators, was conducted after the enrollment of the first 75 patients.
Patients were assessed for outcome events a maximum of three times per week, at the time of planned hemodialysis. Patients who were enrolled before the initiation of routine hemodialysis were assessed regularly in the outpatient clinic. Due to the unique nature of the interaction between dialysis patients and nursing staff, and because all medical care for these patients is delivered in their dialysis center, it is unlikely that any primary or secondary outcomes were missed. Adjudication of the primary outcome event (graft failure) was not performed because this outcome is not subject to observer bias. Adjudication of the secondary outcomes (principally bleeding) was not planned, as we had not anticipated statistically significant differences in these events between the two groups.

To examine the association between baseline prognostic indicators and graft survival, we planned to perform a univariate analysis in which the impact of the baseline variable on the presence or absence of graft failure was determined. The presence or absence of antiplatelet agents and current or planned therapy with dialysis were thought to be strong predictors of the rates of thrombosis; the univariate analysis was therefore stratified by these variables. Multivariate analysis (stratified by these same baseline stratification variables) was then planned to determine which of the baseline variables identified in the univariate analysis maintained their importance in the multivariate analysis.

### Results

#### Patient Characteristics

Between September 1997 and November 2000, 251 patients were screened for study entry and 107 patients (42.6%) were randomized, 56 to receive warfarin (Figure 1). The most common reason for nonentry was patient or family refusal (44 patients; 17.6%). Other major reasons for nonentry were physician refusal (31 patients; 12.4%) and an accepted indication for systemic anticoagulation (30 patients; 12.0%). Forty-four patients (25 allocated to receive warfarin) were receiving ASA at the time of randomization; in all cases, this treatment was

![CONSORT diagram. The flow of patients within the study is presented. Reasons for exclusion are presented in the text.](image)

---

**Table 2. Baseline demographic characteristics for all patients enrolled in the study**

<table>
<thead>
<tr>
<th></th>
<th>Warfarin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (range)</td>
<td>65 (20 to 87)</td>
<td>66 (28 to 85)</td>
</tr>
<tr>
<td>Female gender, n</td>
<td>22</td>
<td>24</td>
</tr>
<tr>
<td>Weight at baseline, kg, mean (range)</td>
<td>80 (51 to 180)</td>
<td>74 (45 to 152)</td>
</tr>
<tr>
<td>History of cardiovascular disease</td>
<td>59%</td>
<td>63%</td>
</tr>
<tr>
<td>Current smoker at time of enrollment</td>
<td>34%</td>
<td>37%</td>
</tr>
<tr>
<td>On antiplatelet therapy at enrollment, n (%)</td>
<td>25 (45%)</td>
<td>19 (37%)</td>
</tr>
<tr>
<td>Underlying renal disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>diabetes</td>
<td>46%</td>
<td>39%</td>
</tr>
<tr>
<td>hypertension</td>
<td>11%</td>
<td>20%</td>
</tr>
<tr>
<td>macrovascular</td>
<td>5%</td>
<td>6%</td>
</tr>
<tr>
<td>glomerulonephritis</td>
<td>9%</td>
<td>16%</td>
</tr>
<tr>
<td>polycystic kidney</td>
<td>5%</td>
<td>2%</td>
</tr>
<tr>
<td>other</td>
<td>23%</td>
<td>18%</td>
</tr>
<tr>
<td>Days of dialysis prior to randomization, median (range)</td>
<td>77 (0 to 6188)</td>
<td>86 (0 to 1627)</td>
</tr>
<tr>
<td>Previous AV graft, n</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Configuration of graft loop</td>
<td>79%</td>
<td>82%</td>
</tr>
<tr>
<td>Baseline laboratory results</td>
<td></td>
<td></td>
</tr>
<tr>
<td>hemoglobin, g/dl (g/L)</td>
<td>10.6 (106)</td>
<td>10.4 (104)</td>
</tr>
<tr>
<td>platelets (×10^9/L)</td>
<td>209</td>
<td>224</td>
</tr>
<tr>
<td>INR</td>
<td>1.1</td>
<td>1.1</td>
</tr>
<tr>
<td>albumin, g/dl (g/L)</td>
<td>3.6 (36)</td>
<td>3.4 (34)</td>
</tr>
</tbody>
</table>

*Among patients on dialysis at time of randomization.*
continued after randomization. Demographic characteristics of study subjects are provided in Table 2.

**Treatment and Follow-Up**

The average achieved INR was 1.45. INR values were above, within, and below the therapeutic range in 9.9%, 47.0%, and 43.1% of cases, respectively (13). Complete follow-up and outcome ascertainment was achieved in all patients. No interim analyses of the study were planned at its outset. As the study progressed it was, however, realized that the rate of graft failure was higher than hypothesized in the *a priori* sample-size calculation. To determine the impact on the sample size, an unplanned interim analysis was performed by an independent, unmasked statistician in June of 1999. The purpose of this analysis was to (1) determine if sample-size adjustment was required on the basis of the observed event rates and (2) to audit the quality of anticoagulation being provided in the warfarin arm. This analysis resulted in the removal of the 4 mg upper dose limit of warfarin (due to inadequate anticoagulation in patients allocated to receive warfarin) and a recommendation to continue the study but to perform a further analysis when an additional 30 patients had been enrolled. This second analysis, performed with data available to October 1, 2000, revealed a statistically and clinically important increase in the risk of major hemorrhage in patients allocated to warfarin. In addition, the point estimate for the effectiveness of warfarin suggested it to be inferior to placebo; as a result, the statistician recommended closure of the study to the steering committee on November 28, 2000.

**Primary Outcome**

The primary analysis included data from all patients from their date of enrollment to their date of censoring, graft loss, or November 28, 2000. Censored patients were as follows: one patient who received a renal transplant with a functioning graft at the time of the transplant, one patient whose graft was removed because of infection, and one patient who developed atrial fibrillation were included in the primary analysis. Comparison of graft survival curves showed non-proportionality (Figure 2) and a nonsignificant trend of efficacy in favor of placebo (log rank *P* = 0.74). As a secondary analysis, the proportion of grafts surviving to the end of the study or censoring was analyzed. Over the study, 41 (73%) of 56 patients allocated to warfarin and 31 (61%) of 51 patients allocated to placebo experienced graft loss (*P* = 0.21; odds ratio [OR] in favor of placebo, 1.76; 95% CI, 0.72 to 4.34; Figure 2). The average time to graft failure was 83 d in the placebo group and 199 d in the warfarin group (*P* = NS). The slightly longer time to graft failure occurring in the context of overall lack of efficacy (as indicated by the proportion of failed grafts) is a consequence of the non-proportional hazards described above. Sixty-two of the grafts that failed did so while they were used for routine hemodialysis, whereas ten failed before first being accessed. Of these ten patients, six were on antiplatelet therapy at the time of enrollment and six were allocated to receive warfarin. Sixty-two of the seventy-two episodes of graft failure occurred in patients who had not prematurely discontinued study drug, and 55 occurred within the first year of treatment. All eight episodes of graft failure after the first year occurred in patients receiving warfarin. Of the 107 patients in the study, 23 patients (12 allocated to warfarin) discontinued study medication before the end of the study. Of these 23, five in the warfarin-treated group and five in the placebo group suffered graft thrombosis after their premature discontinuation. Fourteen patients (7 allocated to warfarin) were receiving study drug at study closure, and five patients who had previously prematurely discontinued study medication (four allocated to warfarin) had functioning grafts at study closure.

**Other Analyses**

The only baseline prognostic indicator associated with graft loss in the intention-to-treat analysis was peripheral vascular disease at enrollment (24% reduction in risk of thrombosis in patients with peripheral vascular disease at baseline; *P* = 0.017); however, the statistical significance of this finding was lost in multivariate analysis. Baseline prognostic indicators that were not associated with risk of thrombosis included gender, location of graft, history of myocardial infarction, stable or unstable angina, stroke, congestive heart failure, venous thromboembolism, valvular heart disease, diabetes, hypertension, hypercholesterolemia, respiratory disease, presence of cancer, and smoking. A non–statistically significant trend toward improved graft survival was seen in patients receiving antiplatelet therapy at the time of randomization: 27 (61%) of 44 patients on antiplatelet therapy experienced graft thrombosis compared with 45 (71%) of 63 patients who were not receiving this therapy (*P* = 0.30; OR, 0.64; 95% CI, 0.3 to 1.4). The proportion of patients with graft thrombosis varied significantly among strata; all 15 of the 15 patients not receiving antiplatelet therapy and not on hemodialysis at the time of randomization experienced graft failure, a significantly higher proportion than that observed in the other three strata (67%, 63%, and 46%; *P* = 0.02).
A secondary, methodologically identical on-treatment analysis was also performed. No differences were observed in the likelihood of survival between the two groups of patients in this secondary analysis. Because the point estimates for graft patency diverged unexpectedly in favor of placebo after the first year of therapy, additional intention-to-treat and on-treatment analyses were performed, confining the analysis to the first year of therapy. No significant differences in graft survival were observed in these analyses. Protocol angioplasty was performed in 20 patients (11 allocated to warfarin). An analysis performed with data censored at the date of angioplasty did not reveal significant alteration in the likelihood of graft survival in each group.

**Adverse Events**

Six major bleeds occurred in 5 patients, all allocated to receive warfarin (one-tailed Fisher exact test for number of patients suffering bleeding, \( P = 0.03 \)) (Table 3). Five of the six bleeds occurred in patients receiving antiplatelet therapy at the time of enrollment, and all five of the patients were receiving antiplatelet therapy at the time of their bleeding event. Eighteen patients (seven allocated to placebo) reported minor bleeding, which was not significantly different between the two treatment arms (\( P = 0.30 \)). Twelve patients (11.2\%) died during the study (seven allocated to placebo; \( P = 0.43 \)).

**Discussion**

This study demonstrates that patients with ESRD who receive warfarin are at significantly increased risk of major hemorrhage compared with patients who receive placebo and that oral anticoagulant administered to achieve an INR of 1.4 to 1.9 was ineffective in this study for the prevention of graft failure. Secondary on-treatment analysis confirmed this finding.

Although warfarin is widely used in patients with PTFE grafts in the hope of maintaining dialysis access (14,15), this study provides the first methodologically rigorous examination of the utility of this therapy. Our finding of no improvement in graft survival is consistent with other recent data. Mokrzycki et al. found no benefit of fixed-dose 1 mg/d warfarin in prevention of thrombosis in dialysis catheters (6). We did observe a nonsignificant, but potentially clinically important, increase in the time to graft failure for patients allocated to warfarin ([199 versus 83 d). This observation warrants further investigation; it is possible that warfarin administered for a finite duration after graft placement (for example, 3 to 6 mo) might prevent early graft loss. Fibrointimal proliferation at the venous anastomosis may play a greater role in late graft loss and is not amenable to warfarin therapy.

The unexpected finding of significant increases in the risk of hemorrhage is novel; previous studies of low-intensity warfarin have not demonstrated a significant increase in the risk of major hemorrhage when compared with patients allocated to ASA or placebo (16). The increased risk of hemorrhage is likely a reflection of the specific characteristics of the dialysis and predialysis patients studied here, which can likely be generalized to hemodialysis populations in North America. This population is elderly, has underlying coagulopathy related to disturbances in the coagulation cascade (17) and uremic platelet dysfunction (14), is frequently prescribed platelet inhibitors for coincident atherosclerotic vascular disease, and receives anticoagulation with intravenous heparin for several hours thrice weekly during dialysis.

Our findings in this study are likely to be valid. The study intervention was randomized, double-blind, and placebo-controlled. Outcome data were available for all patients, and the primary outcome of the study (graft failure) is not subject to observer bias. The primary conclusion of the study was supported by both the intention-to-treat and on-treatment analysis. A limitation of this study is the low achieved INR. However, benefit in previous studies has

**Table 3. Details of major bleeding events**

- **Patient 1:** The patient was admitted to hospital with diarrhea and developed hematemesis while in the emergency department. Upper endoscopy revealed gastric erosions. The patient subsequently became hemodynamically unstable, and a decision to not use aggressive supportive measures was made. The INR at presentation was 1.6. The patient subsequently died.
- **Patient 2:** The patient underwent coronary angiography and became hypovolemic after the procedure. Surgical exploration, evacuation of a 2-L hematoma, and repair of a femoral artery injury was required to control bleeding. The INR at the time of the angiography was 1.4.
- **Patient 3:** The patient was involved in a motor vehicle accident and developed a left cerebral hematoma/contusion and right leg hematoma, which required surgical evacuation. An INR from the time of presentation was not available.
- **Patient 4:** This patient experienced two major bleeds. In the first case, the patient presented with epistaxis, which required hospitalization and cauterization. The INR at the time of presentation was 2.4. Subsequently, the patient was admitted with a decreased level of consciousness and melena. The INR was 1.3 at presentation. The patient was admitted, and over the next 3 d, the hemoglobin fell by 3 g/dl (30 g/L). The patient’s family did not desire investigation, and life support was discontinued.
- **Patient 5:** Patient was hospitalized for gastrointestinal bleeding. Upper gastrointestinal endoscopy showed distal esophageal ulcer and focal erosive gastritis. The hemoglobin fell with this event from 11.1 g/dl to 9.1 g/dl (111 g/L to 91 g/L). The INR at the time of presentation was 1.1.

*All major bleeds occurred in patients allocated to warfarin.*
been obtained with very modest prolongation of INR (12), and in the Medical Research Council’s thrombosis prevention trial, mean INR was 1.47 (18). Furthermore, our observation that the risk of major hemorrhage was significantly increased in patients allocated to warfarin suggests that higher-intensity therapy would be associated with an even more pronounced increase in the risk of hemorrhage.

The overall event rate in our trial was higher than expected. For example, the multicenter Canadian Hemodialysis Morbidity Study observed a 30% graft failure rate in the first year (19). We do not have an adequate explanation for this finding, because a number of different surgeons and centers placed the grafts that were studied in this trial. It is possible that with increased awareness of the importance of placing fistulas when at all possible, those patients who in recent years have had grafts placed have less suitable vascular anatomy than those studied in the early 1990s and subsequently experience worse outcomes than historical controls. This study observed a substantially higher thrombosis rate than that observed by Schwab et al. (10) in 1989, despite using exactly the same monitoring technique and performing angioplasties at a slightly higher rate. It is likely that the prospective thrombosis rate data generated by this study more accurately reflects community experience in the late 1990s. As one of a number of analyses unadjusted for multiple comparisons, we also made the unexpected observation that patients with peripheral vascular disease had a reduced likelihood of thrombotic graft failure; we find this biologically implausible, and do not think weight should be placed on this finding.

In conclusion, this study demonstrates that warfarin administered to achieve an INR of 1.4 to 1.9 is ineffective and potentially dangerous when it is used for the prevention of PTFE dialysis access graft failure, particularly in combination with aspirin. Our findings of an increased risk of major hemorrhage, despite a low achieved INR, further call into question the use of oral anticoagulants for prevention of thrombosis and other types of dialysis access, such as percutaneous catheters. Although more intense anticoagulation (i.e., warfarin administered to achieve a higher target INR) might prevent graft failure, the risk of hemorrhage is likely to be even higher than we observed. On the basis of our results, we recommend that warfarin not be used for primary prophylaxis of thrombosis of PTFE dialysis grafts and cautiously, if at all, for prevention of other dialysis access thrombosis, pending the results of methodologically rigorous studies currently being performed in this patient population. This is particularly true of the use of low-dose warfarin in combination with aspirin, a drug for which many chronic dialysis patients have an accepted indication. We cannot rule out the possibility that warfarin therapy might be of benefit in selected patients at very high risk of thrombosis (such as patients with a hereditary hypercoagulable state or history of recurrent thrombosis), and this area is worthy of further study. For the present, though, our findings suggest that such therapy should be undertaken cautiously in the absence of evidence of efficacy.

Acknowledgments

The warfarin sodium and matching placebo used in this trial were kindly provided by DuPont Pharma. Partial funding for this trial was provided by Physicians Services Incorporated of Ontario, DuPont Pharma, the Father Sean O’Sullivan Research Centre at St. Joseph’s Hospital, the Canadian Institutes for Health Research, the Heart and Stroke Foundation of Canada, Human Resources Development Canada, Regional Medical Associates, and the Nephrology Research fund at McMaster University. Dr. Crowther holds a research Scholarship from the Canadian Institutes for Health Research.

References


Access to UpToDate on-line is available for additional clinical information at http://www.jasn.org/