Effect of dipyridamole plus aspirin on hemodialysis graft patency

Supplemental Appendix:

Subgroup analyses of study treatment heterogeneity and impact of flow monitoring on primary outcome

METHODS

Flow monitoring

Access flow rate was measured using the saline infusion ultrasound dilution technique (Transonic Hemodialysis Monitor HD02, Transonic Systems Inc.).[1, 2] Details of the flow-monitoring procedure and access management algorithm were previously published.[3] Briefly, access blood flow monitoring was initiated as soon as possible but no more than two weeks after starting to use the new access for dialysis. Two measurements of access blood flow were obtained at each visit. A third measurement was obtained if the first two differed by more than 10%. Blood pressure recorded at the time of each access blood flow measurement was used to normalize the measured access blood flow to a standardized mean arterial pressure of 90 mmHg using the equation, nQb = mQb + ((90 – MAP)*8.6), where nQb is the normalized access blood flow, mQb is the measured access blood flow, MAP is the mean arterial pressure and the factor 8.6 is derived from the published regression equation for access flow rate on mean arterial blood pressure.[4, 5] The mean value of the normalized access flow measurements obtained at each visit was used for making algorithm-based decisions regarding referral for angiography.

A second access flow measurement was obtained approximately two weeks after the first. The mean access flow rate for the first two visits constituted the baseline. Monthly measurements of access blood flow were done thereafter until one month after the primary endpoint or study termination. The normalized access flow at each visit was compared to the mean baseline flow to determine if the

subject met criteria for access evaluation. If criteria were met for referral it was recommended that a confirmatory measurement be done as soon as possible, preferably within 2 weeks. If confirmed, the recommendation for angiographic evaluation was based on: 1) a nQb <600 ml/min, or 2) a nQb < 1000 ml/min with a drop of at least 25% below the average of the baseline measurement. These criteria were based on recommendations of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) for vascular access.[6] If angiographic evaluation of the access revealed a stenosis of 50% or more then a corrective procedure was undertaken to reverse the stenosis, which represented an endpoint for the primary outcome.

Statistical analysis

Descriptive statistics were used to compare flow-monitoring outcomes between the randomized treatment assignments. The reason for angiographic evaluation of the study graft was recorded prospectively. Grafts referred for angiography based on flow-monitoring criteria that underwent angioplasty were recorded as flow-monitoring endpoints. Cumulative incidence curves were prepared using a competing risk analysis and used to compare the time course of flow-monitoring endpoints to total cumulative primary endpoints for the study.

Subgroup analyses looking for heterogeneity in study treatment response for the primary outcome were performed as described in the METHODS of the primary manuscript using nine pre-specified variables that have been reported to be risk factors for vascular access failure. A Cox proportional hazard regression model was used. An interaction term between study treatment and the risk factor of interest was included in the model to assess study treatment heterogeneity. All models controlled for baseline use of ACEI or ARB and albumin and stratified by clinical center and access location. For analysis of "center", the models only stratified by access location. For analysis of "access location",

the models only stratified by clinical center. Similarly, adjustment for baseline use of ACEI/ARB or albumin was dropped from the model when analyzing each of these variables, respectively. Follow-up time for the analysis was censored at the earliest occurrence of either the administrative end date of the study, death, transfer to an alternate form of renal replacement therapy or to a clinical center not involved in the trial. All p-values are 2-sided and not adjusted for multiple testing.

The risk attributable to the four pre-specified confounders, clinical center, access location, baseline albumin or use of ACEI/ARB on primary unassisted graft patency was also examined using a Cox proportional hazards model. These models were adjusted for randomized treatment assignment and censored at the earliest occurrence of either the administrative end date of the study, death, transfer to an alternate form of renal replacement therapy or to a clinical center not involved in the trial.

RESULTS

Analysis for heterogeneity in study treatment efficacy

A total of nine pre-specified risk subgroups were selected for the analysis of study treatment heterogeneity. The result for all nine factors is shown in Supplemental Table 1. The point estimate for the HR in each subgroup was less than one and there was no evidence for heterogeneity in study treatment effect as assessed by the interaction term in any of the selected subgroups.

Subgroup analysis of pre-specified confounders on primary unassisted patency

There was a statistically significant effect of clinical center on primary unassisted graft patency. The hazard ratio for the nine clinical centers that randomized more than 10 participants varied from 0.63 to 1.08 (P=0.02). However, there was no statistically significant effect of access location (forearm

vs. other site; HR=1.04, 95% CI 0.85-1.28), baseline use of ACEI or ARB (HR=0.95, 95% CI 0.79-1.14) or baseline albumin (HR=0.88, 95% CI 0.73-1.06) on primary unassisted patency.

Supplementary Table 1. Test for subgroup heterogeneity in study treatment effect

Subgroup	HR (95% CI)[a]	P[b]	P for interaction[c]
Center			
	NA	0.02	0.48
Age			
<=58.6	0.89 (0.68, 1.16)	0.38	0.61
>58.6	0.78 (0.60, 1.01)	0.06	
Gender			
Female	0.77 (0.61, 0.97)	0.03	0.51
Male	0.83 (0.61, 1.13)	0.25	
Race			
Black	0.84 (0.68, 1.04)	0.11	0.56
Other	0.65 (0.44, 0.96)	0.03	
Diabetes			
Presence	0.76 (0.61, 0.96)	0.02	0.84
Absence	0.78 (0.56, 1.09)	0.14	
Access location			
Forearm	0.77 (0.60, 1.00)	0.05	0.54
Upper arm or other	0.87 (0.68, 1.11)	0.26	
Baseline use of ASA			
On	0.92 (0.68, 1.24)	0.57	0.33
Not On	0.76 (0.60, 0.96)	0.02	
Baseline ACEI/ARB			
On	0.93 (0.72, 1.20)	0.57	0.11
Not On	0.72 (0.56, 0.96)	0.02	
Albumin			
>3.7 g/dL	0.75 (0.58, 0.98)	0.03	0.58
≤3.7 g/dL	0.83 (0.64, 1.09)	0.18	

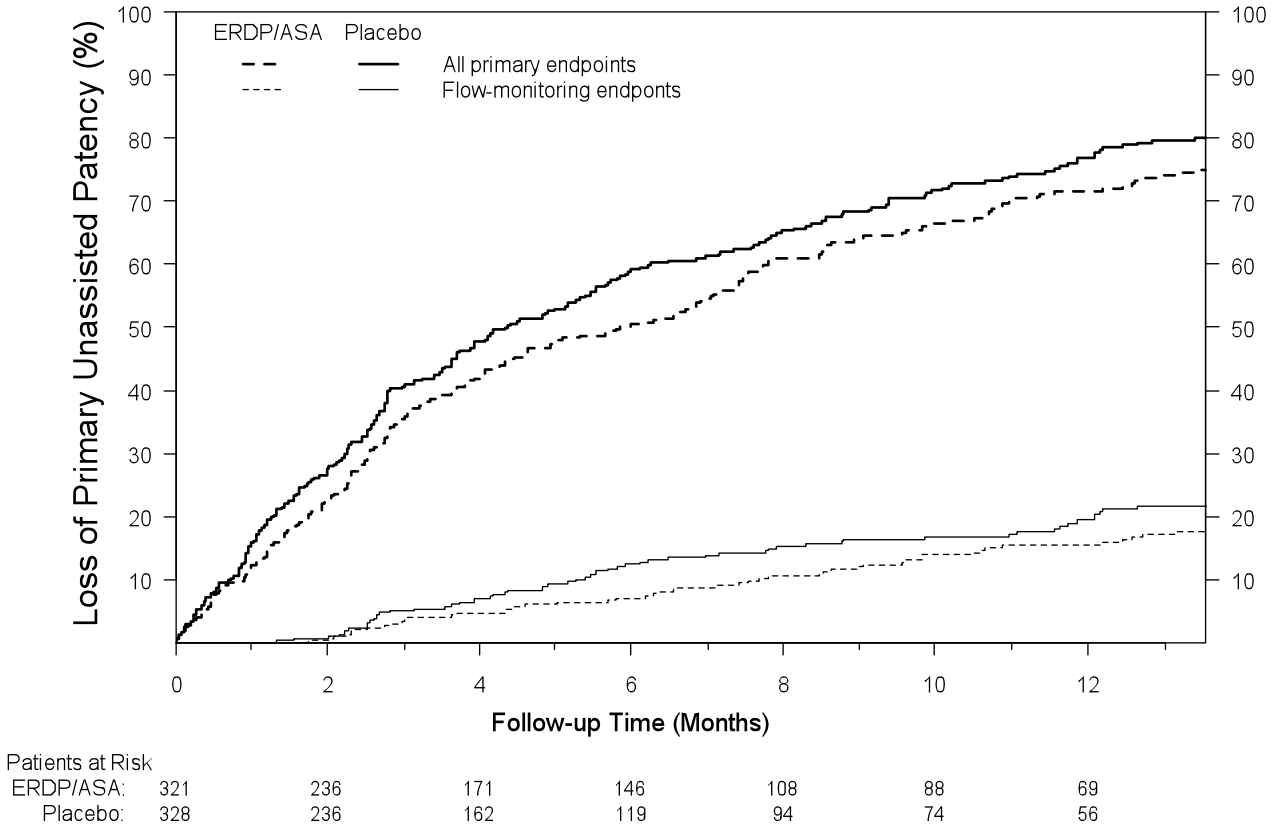
[a]All models control for baseline use of ACEI/ARB and albumin and stratify by center and access location. If the subgroup involves one of these pre-specified variables, then that pre-specified variable is not included in the model.
[b]For "center", P is for testing the center effect on primary unassisted graft patency.
[c]Test for heterogeneity in drug treatment effect on primary outcome for each specified subgroup.

Impact of flow monitoring on primary outcome

Many grafts thrombosed rapidly after access creation before flow monitoring could begin (Supplementary Figure 1). Baseline flow measurements were completed in 176 (54.8%) of patients on ERDP/ASA and 174 (53%) on placebo. There was no difference in the baseline flow measurement between the two groups (mean ± SD = 1168 ± 463 ml/min and 1103 ± 449 ml/min, respectively). Flow monitoring led to referral for angiography in 60 (18.7%) patients on ERDP/ASA and 69 (21%) on placebo at an average (±SD) blood flow of 713 ± 258 ml/min compared to 594 ± 220 ml/min, respectively.

Supplemental Figure 1 shows the cumulative incidence curves for the fraction of primary events occurring directly as a result of flow monitoring in the two treatment groups compared to the total fraction of primary events at each time point. Flow monitoring did not contribute to endpoints until after 6 weeks. In aggregate, flow monitoring accounted for only 24.3% of the 530 total study primary endpoints (23.4% in the ERDP/ASA group and 25.2% in the placebo group).

Flow monitoring accounted for 125 (62.2%) of the 201 endpoints resulting from pre-emptive angioplasty. Other reasons for referral that led to the remaining 76 (37.8%) of pre-emptive angioplasty endpoints included in descending order of frequency: inability to achieve adequate dialysis blood flow, high venous pressure, arm swelling, excessive bleeding after removal of the hemodialysis needle, inability to achieve adequate solute removal (kT/V), a pseudoaneurysm and distal steal syndrome. In some cases more than one reason was identified as the basis for referral. There was no statistically significant difference between the two groups in any of the reasons for referral leading to pre-emptive angioplasty.



Supplementary Figure 1. Cumulative incidence curves for primary endpoints attributed to flow monitoring. The graph demonstrates the cumulative incidence curves for the percent of primary endpoints attributable to flow monitoring (bottom two curves) compared to total endpoints (top two curves) in each treatment group. Endpoints due to flow monitoring in the ERDP/ASA (thin dashed line) and placebo-treated control group (thin solid line) are compared to total endpoints in the ERDP/ASA (thick dashed line) and placebo-treated control group (thick solid line).

DISCUSSION

Primary unassisted graft patency was found to be statistically different between clinical centers. This is consistent with previous studies showing a difference in vascular access patency between surgeons [7] and validates using this as a pre-specified stratification variable in the primary analysis. However, the efficacy of ERDP/ASA to prevent loss of primary patency was not significantly different between the clinical centers. The Cox proportional hazards model used in the present study also stratified by graft location and adjusted for baseline use of ACEI or ARB and serum albumin each of

which has been reported to significantly influence graft patency.[8-10] However, none of these factors were found to have a statistically significant effect on primary unassisted graft patency in the present study.

Participants using ASA represent a subgroup of particular interest.[3] As documented in this trial, use of ASA is increasingly common in this population who often have extensive coexisting cardiovascular disease. Excluding patients on ASA would have seriously limited recruitment and reduced study generalizability. However, the effect of ASA on graft thrombosis or the efficacy of ERDP/ASA was not known.[11-13] In the present trial, the point estimate of the hazard ratio for the primary outcome for participants not on ASA was 0.76 compared to 0.92 for those on ASA at baseline. This difference might reflect a reduced efficacy of ERDP/ASA in patients on ASA or confounding by indication. While we cannot formally exclude an effect of ASA on the efficacy of ERDP/ASA, the interaction term between study treatment and baseline ASA was not statistically significant implying lack of study treatment heterogeneity.

Flow monitoring was incorporated in the study protocol to provide a uniform study-wide approach to meet clinical practice guidelines recommending regular access surveillance to detect stenosis before it leads to graft thrombosis.[14] Moreover, flow monitoring served to focus the study endpoint on the pharmacological target of the intervention, inhibition of access stenosis rather than thrombosis. However, use of flow monitoring also had the potential to increase the observed rate of loss of graft patency.

Flow monitoring demonstrated that the blood flow rate was well matched in the two groups at the time of the first baseline measurement and met criteria for referral in those patients referred for angiography. However, flow monitoring for new grafts was only marginally successful at detecting stenosis before thrombosis. Despite flow monitoring, over 40% of all endpoints were due to

thrombosis. Less than a third of all endpoints were due to pre-emptive angioplasty for stenosis without thrombosis and only 24.3% of all endpoints resulted from referrals based on flow monitoring. The limited efficacy of flow monitoring to prevent thrombosis in these early grafts was due in large part to the high rate of early thrombosis and the lag in initiation of flow monitoring after graft creation (Supplemental Figure 1).

These results imply that flow monitoring did not account for the observed high rate of loss of graft patency. As evidence for this we observed that the hazard rate for loss of primary patency in both treatment groups progressively and uniformly declined after access creation and did not increase as flow monitoring was initiated (data not shown). This suggests that the onset of flow monitoring referrals for angiography after the first 6 weeks did not increase the hazard rate for loss of primary unassisted patency. Moreover, several earlier published studies of graft survival in cohorts of patients who did not undergo this intensive access surveillance also showed the same rate of loss of primary unassisted graft patency seen in the present trial.[9, 15] Taken together, these results imply that flow monitoring in the current protocol had only a modest impact to reduce graft thrombosis and did not account for the observed high rate of loss of primary graft patency.

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