Factors affecting arteriovenous access patency after percutaneous transluminal angioplasty in chronic haemodialysis patients under vascular access monitoring and surveillance: a single-centre observational study

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ABSTRACT

Objectives Maintenance of vascular access (VA) patency after percutaneous transluminal angioplasty (PTA) is important and remains a challenge despite VA monitoring and surveillance. The aim of this study was to examine factors affecting the post-PTA arteriovenous access (AVA) patency in patients who have been on close VA monitoring and surveillance for access flow.

Design Retrospective cohort study.

Setting A single medical centre in Taiwan.

Participants Records of patients who received chronic haemodialysis between 1 January 2017 and 31 December 2018 were retrospectively reviewed. Patients were divided into two groups (without or with PTA intervention on AVA).

Primary and secondary outcome Patients were followed until reintervention PTA, termination or abandoned VA or end of study. In addition to routine monitoring, VA flow surveillance was performed every 3 months for detection of VA dysfunction adhering to Kidney Disease Outcomes Quality Initiative guidelines.

Results A total of 508 patients were selected for study inclusion (with PTA, n=231; without PTA, n=277). At baseline, variables that differed between groups included malignancy and levels of albumin, uric acid, potassium, phosphorous, high-density lipoprotein, total bilirubin and ferritin (all p<0.05). Significant between-group differences were observed for β-adrenergic blocking agents (with PTA, 49.8%; without PTA, 37.5%; p=0.007) and ADP inhibitors (with PTA, 23.8%; without PTA, 11.2%; p<0.001). Among patients with PTA, those with acute myocardial infarction, high ferritin level or arteriovenous graft (AVG) had a significantly higher risk of reintervention post-PTA (p<0.05). Dipeptidyl peptidase-4 inhibitors, thiazolidinediones, ADP inhibitors, and warfarin use were predictors of post-PTA patency (p<0.05).

Conclusions AVG access type, acute myocardial infarction, and high ferritin levels are risk factors for reintervention post-PTA. These findings may be useful in the development of prophylactic strategies for monitoring VA function and tailoring surveillance programs for these dialysis patients.

INTRODUCTION

A successful haemodialysis procedure requires functional vascular access (VA). Haemodialysis VA dysfunction is a major cause of morbidity and hospitalisation in the haemodialysis population.1 Correction of VA dysfunction remains a common procedure in patients undergoing maintenance haemodialysis. The 2006 guidelines of the Kidney Disease Outcomes Quality Initiative (KDOQI)2 recommends the combination of clinical VA monitoring along with access flow surveillance for early identification of potential VA problems to allow for timely intervention. The 2019 update places less emphasis on routine surveillance1; however, surveillance findings remain supplementary to VA monitoring for the purpose of actively identifying and intervening at an early stage. Vascular interventions are recommended when the VA flow is <600 mL/min in grafts and <400–500 mL/min in fistulae and when access flow decreases by 25% and to <1000 mL/min over a 4-month period.3 No clear consensus has been reached regarding the
optimal surveillance technique for identifying failing access. Preventing the development of complications would reduce morbidity, improve quality of life and reduce the cost of healthcare in the dialysis population.

Percutaneous transluminal angioplasty (PTA) is an established standard for the treatment of VA stenosis and can extend the duration of patency in both haemodialysis arteriovenous fistulas (AVF) and arteriovenous grafts (AVG). The duration of patency of PTA is limited and variable, with 12-month postintervention patency rates ranging from 26% to 64%. Recurrent stenosis often requires repeated PTA intervention. Bountouris et al. reported that 50% of AVFs and AVGs requiring PTA ultimately required reintervention. Multiple interventions are often performed to prolong or restore the functional patency of arteriovenous access, requiring an average of 3.1–3.5 procedures before access is abandoned.

Even with clinical monitoring and following surveillance guidelines, maintaining VA after PTA remains a challenge. Further, the KDOQI guidelines have no recommendations on the use of medications for post-PTA patency. The value of medications associated with patency duration after PTA also remains unknown.

This study aims to identify factors affecting post-PTA arteriovenous access patency in routinely monitored patients who were assessed for access flow every 3 months. The identification of specific clinical characteristics, laboratory parameters or medications that affect arteriovenous access patency could allow for more effective monitoring of patients and an improved therapeutic approach post-PTA.

**MATERIALS AND METHODS**

**Study participants**

Records of patients who received chronic haemodialysis at the Shin Kong Wu Ho-Su Memorial Hospital between January 1, 2017 and December 31, 2018 (end of study) were retrospectively reviewed. All haemodialysis patients treated with or without PTA were recruited. Patients were required to have undergone PTA on AVFs or AVGs and were followed until reintervention PTA, termination or abandoned VA or the end of the study. This study was approved by the Institutional Review Board at the Shin Kong Wu Ho-Su Memorial Hospital (20180710R). Due to the retrospective nature of the study, the need for informed consent was waived.

Routine clinical monitoring and access flow surveillance every 3 months for detecting VA dysfunction were conducted according to KDOQI guidelines. Additional PTA interventions were performed according to the KDOQI guidelines under the following circumstances: clinical dysfunction of the AVF or AVG used for haemodialysis or abnormalities of the AVF or AVG on physical examination in conjunction with haemodynamically significant stenosis (>50% diameter reduction) as demonstrated by fistulography. Fistulography was performed in patients with clinical signs such as difficult cannulation, prolonged bleeding after decannulation, upper extremity swelling, repeated high venous pressure volume during dialysis, rapid aneurysm growth or critical flow rate problems.

**Patient and public involvement**

The medical data used for this study were routinely collected, deidentified and retrospective in nature. Therefore, there was no involvement of patient or the public in the design and conduct of the study, choice of outcome measures or recruitment into the study.

**Study characteristics**

A detailed chart review was performed to obtain patient demographic and baseline clinical data (at the time of enrollment, before PTA), including age, sex, comorbid disease history, type of dialysis access, laboratory biochemical parameters (lipid and iron profiles, haemoglobin (Hb), serum albumin, intact parathyroid hormone, sodium, potassium, ionised calcium and phosphate levels, haemodialysis efficiency (Kt/V)) and medication history. The primary study endpoint was post-PTA VA dysfunction. Access dysfunction was defined as the occurrence of reintervention PTA or access failure. Medications prescribed at the time of recruitment were recorded.

**Statistical analysis**

Categorical variables are expressed as the number (N) and percentage, while continuous variables are expressed as the mean and SD. Differences in categorical variables between PTA were examined using the χ² test or Fisher’s exact test, while continuous variables were examined using Student’s t test. Differences in the post-PTA patency according to acute myocardial infarction (AMI), cerebrovascular accident (including stroke and/or haemorrhage but not epileptic seizure), dipeptidyl peptidase (DPP)-4 inhibitors, thiazolidinediones, ADP inhibitor, warfarin or VA type were evaluated using the cumulative curve.

Univariate and multivariate Cox proportional hazards regression analyses were performed to examine post-PTA patency. The multivariate Cox proportional hazards regression model was adjusted for age and sex as confounding factors. Results of the regression analyses are presented as the HR with corresponding 95% CI and p value. All p values were two sided, and p<0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS statistical software V.22 for Windows (IBM, Armonk, New York).

**RESULTS**

**Participant demographic and clinical characteristics**

A total of 556 adult patients on chronic haemodialysis were screened for study eligibility. Forty-eight patients were excluded due to the use of long-term haemodialysis catheters for VA. The final cohort included 231 patients who underwent PTA and 277 patients who did not undergo PTA (figure 1).
Baseline demographic and clinical characteristics of haemodialysis patients with and without PTA are presented in table 1 and online supplemental table 1. Patient age, body mass index and sex were similar between groups. Differences between groups were observed across several variables. Malignancy was significantly higher in patients who did not undergo PTA (14.8%) compared with the PTA group (7.8%; p=0.021). Hb, albumin, uric acid, potassium (K), phosphorous (P) and high-density lipoprotein levels were significantly higher in the PTA group compared with patients who did not undergo PTA (all p<0.039). In contrast, significantly higher total bilirubin and ferritin levels were observed in patients who did not undergo PTA compared with those in the PTA group (all p<0.015). VA type differed significantly between groups (p<0.001); in those patients with AVG access, a higher proportion received PTA intervention (26%) than did not (6.1%). Significant differences between groups were also observed for medication use, including β-adrenergic blocking agents (with PTA, 49.8%; without PTA, 37.5%; p, 0.007) and ADP inhibitors (with PTA, 23.8%; without PTA, 11.2%; p<0.001).

Patients with PTA with and without repeated PTA reintervention differed significantly with respect to ferritin level, VA access type and use of an ADP inhibitor (online supplemental table 2).

### DISCUSSION

This retrospective study identified several factors negatively associated with AV access patency after PTA in patients closely monitored for AV access flow. Factors associated with an increased risk of intervention post-PTA included a history of AMI, increased ferritin levels and the use of AVG access. In addition, the use of specific ADP inhibitors, thiazolidinediones, ADP inhibitor and warfarin as predictors for post-PTA patency (p<0.05) (figure 3A–D).
medications, including β-adrenergic blocking agents, ADP inhibitors and warfarin, was associated with an increased risk of reintervention in patients with PTA. Patients with PTA with and without repeated PTA reintervention differed significantly with respect to ferritin level, VA access type and use of an ADP inhibitor. These findings may provide valuable information for clinicians as they monitor patients for post-PTA access patency.

Several previous studies report factors associated with postintervention AVF patency, including patient age, AVF age, presence of diabetes, length of stenosis and the presence of residual stenosis. AVG patency is negatively associated with diabetes and low levels of serum albumin. Hypertension is positively associated with patency in patients with AVF and AVG. In addition, patients with AVG access have a greater risk of patency loss than those with AVF. However, few studies have compared post-PTA patency between patients with AVF and AVG access. Our findings show that patients with AVG access have a higher risk of post-PTA intervention than do patients with AVF access. This finding is consistent with a previous study reporting that post-PTA primary and secondary patency rates were significantly higher in patients with AVF than AVG access.

A higher incidence of AMI was reported in patients with access failure, and a history of cardiovascular disease (including myocardial infarction) is a risk factor for patency loss. For patients with a history of cardiovascular disease such as AMI, the pre-existing vascular pathology of the vessels used to create access likely results in inferior access patency. Haemodialysis patients in poor vascular condition are more prone to arterial calcification during dialysis, resulting in stenosis and thrombosis. These pre-existing pathological changes

| Variables                      | Univariate analysis | Multivariate analysis |
|-------------------------------|---------------------|----------------------|
|                               | HR (95% CI)         | P value              |
|                               |                     | HR (95% CI)          | P value |
| Comorbidity predictors        |                     |                      |
| AMI                           | 2.18 (1.45 to 3.28) | <0.001               |
|                               |                     | 2.17 (1.45 to 3.24)  | <0.001  |
| Lab data predictors           |                     |                      |
| Ferritin (ng/mL)              | 3.52 (1.17 to 10.62) | 0.025               |
| VA type*                      | 1.66 (1.18 to 2.34) | 0.004               |
|                               |                     | 1.65 (1.17 to 2.33)  | 0.005   |
| Medication predictors         |                     |                      |
| DPP-4 inhibitors              | 1.57 (1.08 to 2.28) | 0.017               |
| Thiazolidinediones            | 2.65 (1.27 to 5.55) | 0.010               |
| ADP inhibitor                 | 1.88 (1.31 to 2.70) | 0.001               |
| Warfarin                      | 2.22 (1.25 to 3.92) | 0.006               |

Parameter measured in *205 subjects. Bold text indicates statistical significance, p-value < 0.05.

*Multivariate analysis with age, sex and significant variables from univariate analysis as confounding factors.

AMI, acute myocardial infarction; DPP-4, dipeptidyl peptidase IV; PTA, percutaneous transluminal angioplasty; VA, vascular access.

Figure 2 Cox regression survival plot indicating cumulative curve for patients after an initial successful PTA according to (A) a history of acute myocardial infarction (AMI), and (B) type of vascular access: arteriovenous fistula (AVF) or arteriovenous graft (AVG).
contribute to AVF patency loss in patients on long-term haemodialysis. This sequelae explains our observation that a history of AMI increases the risk of post-PTA intervention.

Serum ferritin, an indicator of iron storage, may be elevated in chronic inflammatory conditions. We observed that elevated ferritin level is associated with post-PTA patency loss. In haemodialysis patients, high serum ferritin is associated with atherosclerosis and coronary arterial stenosis. This study is the first to identify serum ferritin as a potential biomarker for predicting post-PTA patency. High ferritin levels are associated with early thrombosis and venous stenosis in haemodialysis patients with AVF access. We speculate that patients with elevated ferritin levels are more prone to pathological conditions such as arteriosclerosis involving vascular intimal hyperplasia. This condition is a common pathological finding in thrombosis caused by venous–stenosis-related access failure.

While diabetes mellitus was not associated with post-PTA patency in our study, medications taken for type 2 diabetes mellitus (DPP-4 inhibitors and thiazolidinediones) increased the risk of post-PTA intervention. To the best of our knowledge, no studies have reported a direct association between the use of DPP-4 inhibitors and VA patency. Thiazolidinedione induces adiponectin production, resulting in a vasculoprotective decrease in smooth muscle cell proliferation and inflammation and an increase in nitric acid release. These processes have been shown to inhibit AVG stenosis in a porcine AVG model.

Whether diabetes and hypertension influence postintervention patency remains controversial. Several studies suggest that diabetes and hypertension are not associated with patency after PTA, while others report that diabetes is an important risk factor for fistula restenosis, another reports that diabetes is associated with lower AVG patency but has no relationship with AVF patency. We speculate that our finding that DPP-4 inhibitors and thiazolidinedione are negatively associated with post-PTA patency could be due in part to patient comorbidities and clinical conditions (eg, poorly controlled hyperglycaemic) rather than a direct effect on vascular patency. Our study did not investigate the glycaemic state of patients.

We observed that the use of ADP receptor inhibitors (antiplatelet medications) is associated with AVF failure. However, patients taking ADP inhibitors may be more prone to thrombosis due to comorbid conditions or other

Figure 3 Cox regression survival plot indicating cumulative curve for patients after an initial successful percutaneous transluminal angioplasty (PTA) according to medication use: (A) dipeptidyl peptidase-4 (DPP4) inhibitor, (B) thiazolidinedione (TZD), (C) ADP receptor inhibitor and (D) warfarin.
factors. Results of a meta-analysis of 10 trials revealed that antiplatelet agents reduced the rate of AVF thrombosis but not AVG thrombosis. Another meta-analysis reported a protective effect of antiplatelet treatment against thrombosis or loss of patency, although little effect was seen on graft patency. In contrast, a retrospective study of 901 patients concluded that treatment with antiplatelet medications was associated with significantly worse AVF patency. A retrospective, longitudinal cohort study of AVF patients investigated the association between AVF primary patency and the use of antiplatelet agents, antihypertensive agents, nitrates and nitrites, statins, dipryidamole and pentoxifylline. Of these medications, only dipryidamole showed a significant association with a higher risk of AVF patency loss, in particular, when combined with antiplatelet agents.

Several clinical investigations and trials have reported that statins, anticoagulants (warfarin) and antiplatelet drugs can reduce thrombosis and improve VA outcomes. However, inconsistencies remain regarding the effectiveness of prophylactic drugs in reducing the risk of VA failure. Anticoagulation therapy (heparin) administered during AVF surgery was examined in two randomised studies to evaluate postsurgical patency. Intravenous heparin administration was associated with an increased incidence of bleeding complications and no benefit in terms of AVF patency. Increased bleeding has been reported by others, specifically, in patients with end-stage renal disease and polytetrafluoroethylene dialysis grafts who were treated with warfarin. Their results were similar to other studies, in that low-dose warfarin was associated with an excess of clinically important major bleeding in patients with ESRD; in addition, warfarin did not appear to prolong PTFE graft survival.

While standard PTA was the predominant angioplasty method used to treat patients in our cohort, a small number underwent drug-coated balloon (DCB) angioplasty. A meta-analysis of studies comparing these methods for the treatment of dysfunctional haemodialysis venous access concluded that DCB is favoured over PTA. Based on these findings, postintervention patency was likely greater among patients who underwent DCB angioplasty in our study. Because a very small fraction of our patients underwent DCB, we are confident that our results were not affected by this inconsistency. Further study of whether DCB alters the factors that affect post-PTA reintervention is warranted.

Together, these findings suggest that few prophylactic drugs effectively prevent VA failure for AVF and AVG, and no strong evidence indicates the efficacy of any medications in reducing the incidence of VA failure. Regardless, our study suggests that the use of the prescribed medications alone or in combination may not always have a beneficial effect on vascular patency.

Limitations
This single-centre study is non-randomised and retrospective in nature. Thus, information regarding the reason for prescribed medications, medication doses, dates of treatment initiation and treatment duration were not available. A history of medication use likely reflects patient comorbidities, indicating potential bias caused by the presence of multiple risk factors, regardless of the PTA. The cohort was small, and the follow-up period was short. Poor vascular anatomy and lesions may affect patency outcomes but were not assessed in this study.

CONCLUSIONS
Despite well-established clinical monitoring guidelines, vascular patency after angioplasty is still highly variable. We identified AVG access type, AMI and high ferritin levels as risk factors for reintervention post-PTA. These results suggest that in addition to clinical monitoring, proactive surveillance of VA flow after PTA is prudent. Our findings may be useful in the development of prophylactic strategies for monitoring VA and tailoring surveillance programmes for dialysis patients.

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Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the Institutional Review Board at the Shin Kong Wu Ho-Su Memorial Hospital (IRB Number 20180710R). The informed consent was waived by the Institutional Review Board at the Shin Kong Wu Ho-Su Memorial Hospital in view of the retrospective nature of the study.

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