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Original Article

ORIGINAL ARTICLE

Arteriovenous fistula thrombosis is associated with increased all-cause and cardiovascular mortality in haemodialysis patients from the AURORA trial

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ABSTRACT

Background. The impact of arteriovenous fistula (AVF) or graft (AVG) thrombosis on mortality has been sparsely studied. This study investigated the association between AVF/AVG thrombosis and all-cause and cardiovascular mortality.

Methods. The data from 2439 patients with AVF or AVG undergoing maintenance haemodialysis (HD) included in the A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events trial (AURORA) were analysed using a time-dependent Cox model. The incidence of vascular access (VA) thrombosis was a pre-specified secondary outcome.

Results. During follow-up, 278 AVF and 94 AVG thromboses were documented. VA was restored at 22 ± 64 days after thrombosis (27 patients had no restoration with subsequent permanent central catheter). In multivariable survival analysis adjusted for potential confounders, the occurrence of AVF/AVG thrombosis was associated with increased early and late all-cause mortality, with a more pronounced association with early all-cause mortality {hazard ratio [HR] < 90 days 2.70 [95% confidence interval (CI) 1.83–3.97], $P < 0.001$; HR > 90 days 1.47 [1.20–1.80], $P < 0.001$}. In addition, the occurrence of AVF

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thrombosis was significantly associated with higher all-cause mortality, whether VA was restored within 7 days [HR 1.34 (95% CI 1.02–1.75), P = 0.036] or later than 7 days [HR 1.81 (95% CI 1.29–2.53), P = 0.001].

Conclusions. AVF/AVG thrombosis should be considered as a major clinical event since it is strongly associated with increased mortality in patients on maintenance HD, especially in the first 90 days after the event and when access restoration occurs >7 days after thrombosis. Clinicians should pay particular attention to the timing of VA restoration and the management of these patients during this high-risk period. The potential benefit of targeting overall patient risk with more aggressive treatment after AVF/AVG restoration should be further explored.

Keywords: arteriovenous fistula, arteriovenous graft, cardiovascular mortality, chronic haemodialysis, survival, vascular access complication

INTRODUCTION

Vascular access (VA) is the 'lifeline' of patients on chronic haemodialysis (HD). However, it is also the source of specific complications, such as bleeding and infections (either local or systemic), and requires urgent intervention, particularly in cases of thrombosis [1]. Native arteriovenous fistula (AVF) is currently the best VA when technically feasible, according to the international dialysis guidelines [2–4]. Their use is associated with better patient survival compared with arteriovenous graft (AVG) or catheters [2]. Mechanisms leading to stenosis or thrombosis of AVF/AVG are poorly elucidated. In particular, the contribution of systemic factors (age, hypercoagulability, chronic inflammation, poor vascular state etc.) in addition to local factors (i.e. initial surgical procedure, quality of the anastomosis, mechanical lesions linked to repeated cannulations etc.) is uncertain [5, 6].

Cardiovascular (CV) disease is a major cause of mortality in dialysis. Although CV mortality has decreased among dialysis patients in the past decades [7], the rate of CV outcome of these patients is still dramatically higher than the general population. Classical therapeutic interventions such as statins have failed to improve CV mortality in dialysis and classical scores are suboptimal in predicting mortality in dialysis.

To date, no study has investigated the impact of AVF/AVG failure on mortality among patients on HD. While VA failure may increase mortality by way of poor dialysis adequacy or complications related to revascularization, it is our hypothesis that such failure, especially with AVF, is a marker of poor general state: AVF/AVG thrombosis could consequently serve as an integrative short- and midterm risk stratifier in HD patients. Whether AVF/AVG failure represents an important risk stratifier may have substantial clinical implications since it could promote a closer follow-up after restoration of VA access, with possibly a more aggressive treatment not limited to VA access restoration also targeting overall patient risk.

In light of the above, this study aimed to assess the association between VA complications with all-cause and CV mortality in dialysis patients from the large multicentre, randomized control A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events (AURORA), which recorded VA failure as a pre-specified secondary outcome [8, 9].

MATERIALS AND METHODS

Study population

Analyses were performed on the AURORA data for which results have previously been reported [8–10]. The study obtained institutional review board approval. Briefly, the AURORA was a randomized, double-blind, placebo-controlled, multicentre study involving 2776 patients, 50–80 years of age, who were undergoing maintenance HD for at least 3 months (ClinicalTrials.gov number NCT00240331). After providing written informed consent, patients were randomly assigned to receive rosuvastatin, 10 mg daily or placebo. Exclusion criteria are detailed in the supplementary data. For this analysis, patients with a tunnelled central venous dialysis catheter ($n = 316$) or with missing data regarding VA ($n = 21$) were excluded. During a median follow-up period of 3.8 years, the initiation of treatment with rosuvastatin had no significant effect on the composite primary endpoint of death from CV causes, non-fatal myocardial infarction or non-fatal stroke {hazard ratio [HR] 0.96 [95% confidence interval (CI) 0.84–1.11]}. Rosuvastatin also exhibited no significant effects on the incidence of procedures as a result of stenosis or thrombosis of the VA for long-term dialysis (AVF and AVG only) compared with placebo [HR 1.10 (95% CI 0.95–1.27)], the latter constituting one of the pre-specified secondary endpoints of the trial. All events recorded during the trial were reviewed and adjudicated by a clinical endpoint committee to ensure consistency of the event diagnosis.

Definition of stenosis and thrombosis

As pre-specified by the protocol [8], a corrective procedure for VA thrombosis was considered as the intervention required upon occurrence of VA failure. This excluded saline or heparin flushing while including the following: thrombolysis, angioplasty with or without stent, surgical refashioning and new access site creation.

Statistical analysis

Statistical methods are detailed in the supplementary data. Briefly, statistical analyses were performed using Statistical Package for the Social Sciences, SPSS version 22 software (IBM, Armonk, NY, USA). Descriptive statistics are reported as percentages for categorical variables and mean ± SD for continuous variables. Comparisons of baseline characteristics were carried out using *t*-test, analysis of variance or chi-squared tests as required. VA thrombosis-free survival was calculated using the Kaplan–Meier formula and survival curves plotted accordingly. Associations between baseline characteristics and the occurrence of thrombosis during follow-up and between the occurrence of thrombosis during follow-up and all-cause mortality or CV mortality were assessed using the Cox proportional hazards model. VA thrombosis was used as a time-dependent variable. Moreover, since a significant interaction with time was identified, separate Cox models were fitted for the following time intervals: <90 and >90 days after the VA thrombosis. Finally, to better assess the impact of the timing of VA restoration on outcome, the association of VA thrombosis with VA restoration within 7 days and later than 7 days was evaluated by creating

Table 1. Baseline characteristics and recorded outcomes of patients with VA thrombosis during follow-up in comparison with patients with no VA complications according to VA type

	AVF ($N = 2199$)			AVG ($N = 240$)		
Characteristics	No thrombosis ($n = 1921$)	Thrombosis ($n = 278$)	P-value	No thrombosis ($n = 146$)	Thrombosis ($n = 94$)	P-value
Baseline characteristics						
Age (years)	63.78 ± 8.71	64.69 ± 8.46	0.10	63.38 ± 8.33	64.61 ± 8.14	0.26
Years on RRT	4.52 ± 5.20	4.49 ± 5.33	0.93	6.12 ± 6.47	5.68 ± 6.35	0.60
Measured K_t/V	1.44 ± 0.56	1.43 ± 0.59	0.82	1.49 ± 0.41	1.42 ± 0.33	0.17
Albumin (g/L)	39.98 ± 3.40	39.48 ± 3.44	**0.02**	39.57 ± 3.08	39.33 ± 2.77	0.54
Haemoglobin (g/dL)	11.69 ± 1.61	11.70 ± 1.49	0.87	11.79 ± 1.57	11.84 ±1.50	0.81
hs-CRP (mg/L)	0.95 ± 1.12	1.04 ± 1.21	0.24	1.10 ± 1.21	1.18 ± 1.35	0.62
BMI (kg/m^2)	25.27 ± 4.64	24.93 ± 4.47	0.24	25.48 ± 5.43	26.22 ± 5.91	0.32
SBP (mmHg)	137.96 ± 24.22	132.22 ± 22.93	**<0.001**	140.12 ± 26.19	125.24 ± 23.61	**<0.001**
DBP (mmHg)	76.20 ± 12.62	74.41 ± 12.41	**0.03**	76.94 ± 12.41	70.02 ± 12.58	**<0.001**
Male gender (%)	66.0	62.6	0.28	43.2	51.1	0.24
Current smoker (%)	15.2	14.0	0.65	24.0	9.6	**0.006**
Diabetes (%)	25.0	24.1	0.77	24.7	27.7	0.65
Peripheral artery disease (%)	13.7	18.7	**0.03**	18.5	19.1	1.00
History of coronary disease	12.1	10.1	0.37	16.4	19.1	0.60
Platelet inhibitors (%)	41.4	38.1	0.33	61.0	53.2	0.28
Rosuvastatin (%)	49.8	48.2	0.65	50.0	59.6	0.19
Intervention for VA complication, *n* (%)						
Thrombolysis	N/A	48 (17.3)	N/A	N/A	25 (26.6)	N/A
Angioplasty ± stent		33 (11.9)			15 (16.0)	
Surgical refashioning		69 (24.8)			29 (30.9)	
New access needed		125 (45.0)			25 (26.6)	
Unknown		3 (1.1)			0 (0)	
Number of deaths, *n* (%)	835 (43.5)	127 (45.7)	N/A	77 (52.7)	46 (48.9)	N/A
<90 days after thrombosis, *n* (%)	N/A	28 (10.1)	N/A	N/A	5 (5.3)	N/A
>90 days after thrombosis, *n* (%)	N/A	99 (35.6)	N/A	N/A	41 (43.6)	N/A
Cause of death, *n* (%)						
Coronary heart disease	273 (32.7)	33 (26.0)	N/A	17 (22.1)	15 (32.6)	N/A
Other cardiac cause	44 (5.3)	7 (5.5)	N/A	4 (5.2)	3 (6.5)	N/A
Other vascular cause	62 (7.4)	12 (9.4)	N/A	6 (7.8)	2 (4.3)	N/A
Other CV cause	1 (0.2)	0 (0)	N/A	0 (0)	0 (0)	N/A
Stroke	49 (5.9)	8 (6.3)	N/A	3 (3.9)	3 (6.5)	N/A
Non-CV cause	320 (38.3)	60 (47.2)	N/A	35 (45.5)	20 (43.5)	N/A
Non-adjudicated death	86 (10.3)	7 (5.5%)	N/A	12 (15.6)	3 (6.5)	N/A

Results with p value less than 5% were emphasized using bold letters.
BMI, body mass index; N/A, not applicable; RRT, renal replacement therapy.

two time-dependent variables. Survival analyses were also carried out separately according to the VA type.

Finally, analyses were also conducted for the composite primary endpoint of the AURORA (composite endpoint of death from CV causes, non-fatal myocardial infarction or non-fatal stroke).

RESULTS

Baseline characteristics of patients according to the type of vascular access (arteriovenous fistula or arteriovenous graft) and the presence of a thrombosis of the vascular access during follow-up

Patients with AVF ($n = 2199$) differed from patients with AVG ($n = 240$) for several baseline factors. Other than AVF patients being more frequently male (65.6 versus 46.2%; $P < 0.001$), AVG patients had more CV risk factors, including more frequent ischaemic heart disease (17.5 versus 11.9%; $P = 0.02$), longer dialysis duration (5.95 ± 6.42 years versus 4.52 ± 5.21; $P = 0.001$) and higher high-sensitivity C-reactive protein (hs-CRP) (1.13 ± 1.26 mg/L versus 0.96 ± 1.13; $P = 0.05$).

In AVF patients, those experiencing thrombosis requiring a procedure had a more frequent history of peripheral arterial disease than those without VA complication (Table 1; $P = 0.03$). Both systolic (SBP) and diastolic blood pressure (DBP) were lower in patients with thrombosis. The baseline serum albumin level was lower in patients with AVF experiencing thrombosis during follow-up. Likewise, in AVG patients, SBP and DBP were markedly lower in patients with thrombosis ($P < 0.001$). The proportion of current smokers was surprisingly lower in the group of AVG patients with thrombosis ($P = 0.006$).

Baseline predictors of the thrombosis of the vascular access (arteriovenous fistula or arteriovenous graft) during follow-up

A total of 94 AVG thromboses and 278 AVF thromboses were documented during follow-up. Patients with AVG had a higher risk of thrombosis (Figure 1; $P < 0.001$). In multivariable analysis, baseline characteristics associated with an increased rate of VA thrombosis during follow-up were VA type [AVG versus AVF: HR 4.79 (95% CI 3.70–6.19); $P < 0.001$], older age, lower SBP,

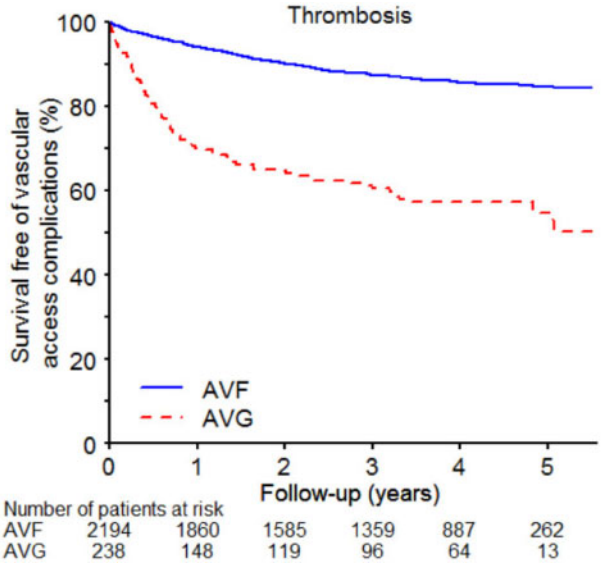

FIGURE 1: Death-censored survival free of VA complications during follow-up according to the type of VA (AVF or AVG).

hypoalbuminaemia and platelet inhibitor medication. In AVF patients, older age, hypoalbuminaemia and lower SBP were associated with increased risk of AVF thrombosis. In the AVG group, only a lower SBP was significantly associated with increased risk of VA thrombosis. Although associated with CV outcomes (data not shown), hs-CRP was not associated with the risk of AVF/AVG thrombosis. Predictors of VA thrombosis in multivariable models for all patients and according to VA type are presented in Supplementary data, Table S1.

Associations between the complications of the vascular access (arteriovenous fistula or arteriovenous graft) and outcomes

Given the significant interaction with time for all-cause mortality (P = 0.005) and CV mortality (P = 0.038), the associations between thrombosis and mortality were expressed according to two time periods (<90 or >90 days after AVF/AVG thrombosis). During the follow-up, 1085 deaths were recorded, 962 among patients with AVF and 123 among patients with AVG (Table 1). As shown in Figure 2 (and in Supplementary data, Table S2), in multivariable analysis, AVF/AVG thrombosis was associated with increased early (<90 days) all-cause mortality [HR 2.70 (95% CI 1.83–3.97), P < 0.001] and, to a lesser extent, with late (>90 days) all-cause mortality [HR 1.48 (95% CI 1.20–1.79), P < 0.001]. Similar results were observed for CV mortality as well as for the composite endpoint of death from CV causes, non-fatal myocardial infarction or non-fatal stroke.

Associations between the thrombosis of the vascular access (arteriovenous fistula or arteriovenous graft) and mortality

AVF thromboses were strongly associated with early and late all-cause mortality [HR 3.07 (95% CI 2.01–4.71), P < 0.001 and HR 1.50 (95% CI 1.19–1.88), P = 0.001, respectively]. No significant association was observed between AVG thrombosis and mortality [HR for early all-cause mortality = 1.70 (95% CI 0.67–4.34), P = 0.27 and HR for late all-cause mortality = 1.31 (95% CI 0.83–2.05), P = 0.25]. There was no significant interaction between VA type and VA thrombosis (P for interaction >0.20 for both early and late all-cause mortality).

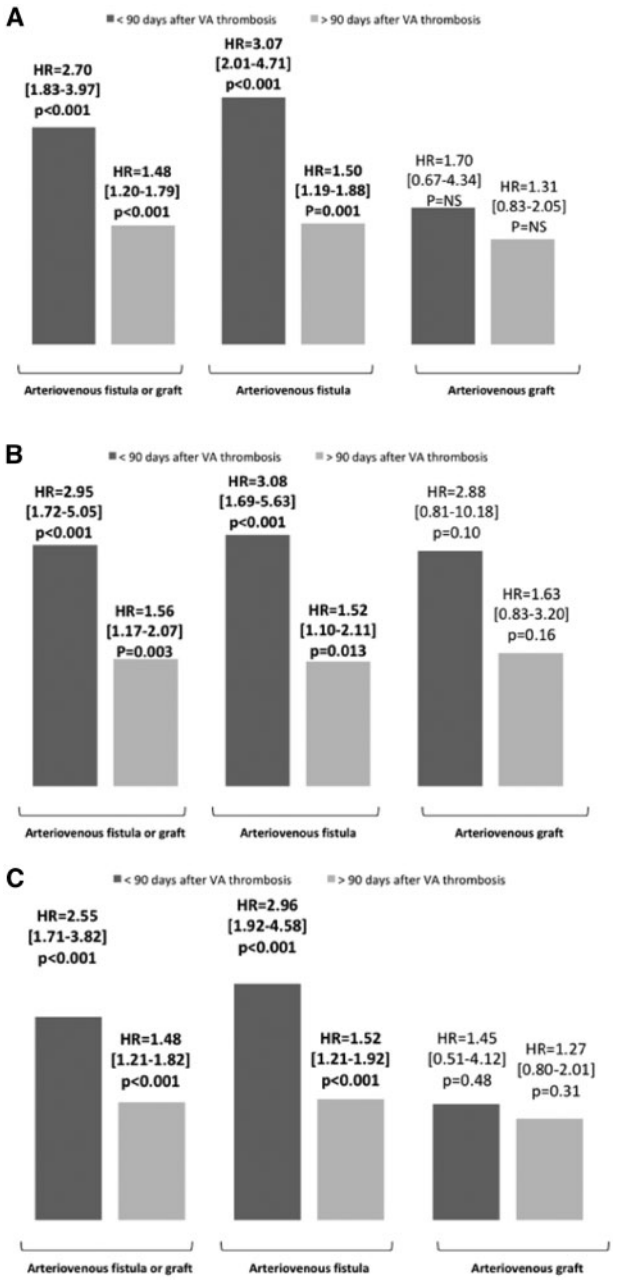

FIGURE 2: Association in multivariable analysis [adjusted for age, gender, years on RRT, type of VA (when applicable), current smoking, diabetes, history of coronary disease, history of peripheral arterial disease, BMI, systolic blood pressure, calculated K_t/V, albumin level, haemoglobin level and hsCRP level (at baseline), platelet inhibitors and rosuvastatin] between VA complications and (**A**) all-cause and (**B**) CV mortality, as well as on (**C**) the composite endpoint of death from CV causes, non-fatal myocardial infarction or non-fatal stroke according to type of VA and type of complication. Results are presented as HR with 95% CIs. NA, not available.

Associations between the thrombosis of the vascular access (arteriovenous fistula or arteriovenous graft) and mortality according to the timing of the vascular access restoration

The association of AVF/AVG thrombosis on mortality was evaluated in instances of early (<7 days) or delayed (>7 days) AVF/

Table 2. Impact of VA thrombosis and time to VA restoration (< or >7 days) on all-cause mortality according to VA type

	All patients (events, $n = 959$)		AVFs (events, $n = 846$)		AVGs (events, $n = 113$)	
Variables	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (years)	1.04 (1.03–1.05)	**<0.0001**	1.04 (1.03–1.05)	**<0.0001**	1.05 (1.02–1.08)	**<0.0001**
Time on RRT (for 1 year)	1.01 (1.00–1.03)	0.07	1.01 (1.00–1.03)	0.08	1.01 (0.98–1.05)	0.43
Albumin (for 1 g/L)	0.96 (0.94–0.98)	**<0.001**	0.95 (0.93–0.97)	**<0.001**	1.02 (0.94–1.10)	0.66
Haemoglobin (for 1 g/dL)	0.94 (0.90–0.98)	**0.003**	0.94 (0.90–0.98)	**0.004**	0.90 (0.78–1.03)	0.13
One log increase in hs-CRP	1.24 (1.17–1.31)	**<0.001**	1.24 (1.17–1.32)	**<0.001**	1.19 (1.02–1.40)	**0.027**
BMI (for one kg/m^2)	0.98 (0.97–0.99)	**0.015**	0.98 (0.97–1.00)	**0.048**	0.97 (0.93–1.02)	0.23
SBP (for one mmHg)	1.00 (1.00–1.01)	0.08	1.00 (0.99–1.01)	0.11	1.00 (0.99–1.01)	0.49
Male gender	0.89 (0.77–1.03)	0.11	0.90 (0.78–1.05)	0.19	0.83 (0.54–1.27)	0.40
Current smoking	1.28 (1.07–1.53)	**0.007**	1.34 (1.11–1.63)	**0.003**	0.97 (0.57–1.66)	0.91
Diabetes	1.55 (1.34–1.80)	**<0.001**	1.51 (1.29–1.77)	**<0.001**	1.92 (1.25–2.96)	**0.003**
Peripheral artery disease	1.33 (1.13–1.57)	**0.001**	1.39 (1.16–1.66)	**<0.001**	1.07 (0.66–1.74)	0.78
History of coronary disease	1.43 (1.20–1.71)	**<0.001**	1.43 (1.18–1.73)	**<0.001**	1.43 (0.89–2.29)	0.14
K_t/V	0.65 (0.50–0.84)	**0.001**	0.66 (0.50–0.87)	**0.003**	0.59 (0.26–1.36)	0.22
AVG (AVF is reference group)	1.04 (0.84–1.28)	0.71	–	–	–	–
Platelet inhibitors	1.07 (0.93–1.22)	0.34	1.08 (0.94–1.25)	0.27	0.94 (0.60–1.47)	0.79
Rosuvastatin	0.99 (0.88–1.13)	0.94	0.98 (0.86–1.13)	0.83	1.06 (0.72–1.58)	0.76
Thrombosis with restoration of the VA in <7 days	1.26 (1.00–1.59)	**0.049**	1.34 (1.02–1.75)	**0.036**	1.06 (0.66–1.70)	0.82
Thrombosis with restoration of the VA in >7 days	1.78 (1.29–2.38)	**<0.001**	1.81 (1.29–2.53)	**0.001**	1.37 (0.62–3.06)	0.44

BMI, body mass index; RRT, renal replacement therapy.
Results with p value less than 5% were emphasized using bold letters.

AVG restoration. Of note, AVF/AVG thrombosis was significantly associated with all-cause mortality when AVF/AVG restoration occurred both within 7 days and later than 7 days, although the association was more pronounced when AVF/AVG restoration occurred later [HR 1.26 (95% CI 1.00–1.59) and HR 1.78 (95% CI 1.29–2.38), respectively]. Similar associations were also observed in AVF patients.

DISCUSSION

To the best of our knowledge, this study is the first to assess the association between AVF/AVG thrombosis and mortality. In this large multicentre randomized controlled trial, AVF/AVG thrombosis was found to be associated with high mortality, in particular for early all-cause and CV mortality following thrombosis. Of note, the association with increased long-term mortality risk, while mitigated, also persisted even in instances of rapid AVF/AVG restoration performed within a delay of 7 days. These results suggest that AVF/AVG thrombosis should be considered as a major clinical event. In addition, particular attention should likely be paid to the timing of AVF/AVG restoration as well as the short- and midterm management of these patients following AVF/AVG thrombosis.

Evidence of an impact of vascular access failure on survival

In international guidelines [2, 3], prevention of VA dysfunction is recommended in order to avoid underdialysis as well as to prevent thrombosis. Clinical trials have assessed the impact of active VA surveillance and preventive interventions for VA stenosis on VA survival, but not on patient survival [11]. Nonetheless, two large studies [12, 13] have reported that conversion from a permanent VA to a catheter is associated with increased mortality, thus indirectly suggesting an impact of VA failure on mortality. This study accordingly indicates a strong association of VA thrombosis on patient survival.

Vascular access thrombosis is associated with increased mortality: pathophysiological hypotheses

Various mechanisms may explain poor short-term survival following VA thrombosis, including hydroelectrolytic abnormalities related to the incapacity to perform a dialysis session, the need for a temporary catheter, complications associated with central catheter placement [14] as well as the revascularization procedure. The primary complications of endovascular angioplasty and thrombectomy include vein rupture, pulmonary embolism and peripheral arterial embolization [15]. However, the reported complication rates have been low, with the latter being of minor severity in most instances [15, 16]. Such immediate complications are likely not responsible for the increase in long-term CV mortality observed in this study.

Long-term use of a central catheter as a VA is a well-known factor associated with an increased risk of mortality in dialysis [17]. Importantly, considering that the increased risk of mortality is observed even in the case of rapid or immediate VA restoration (<7 days), the association between VA failure and mortality would suggest that the latter is not solely the consequence of long-term dialysis inadequacy [18] or the deleterious impact of long-term central catheter use as a VA [17].

VA thrombosis is likely a risk marker, that is, a consequence of risk factors yet to be identified, associated with poor CV outcome. Increased coagulation activation has been observed in dialysis patients and may be partially involved in VA complications [6]. VA thrombosis is also putatively related to systemic pathological conditions, as highlighted by the decrease in serum albumin level and weight loss, which could account for an increased CV mortality [13]. However, hs-CRP, which was previously shown to be a strong predictor of CV outcome [19, 20], was not associated with VA thrombosis in this

study. Uremic vasculopathy could also be involved, having been highlighted in both the pathophysiology of VA maturation failure and stenosis/thrombosis [21, 22] as well as evoked in increased CV mortality observed in end-stage renal disease (ESRD) [23, 24]. Specifically, as part of the histological findings of the large prospective multicentre Hemodialysis Fistula Maturation Cohort Study, Alpers *et al.* [25] recently reported that luminal narrowing was more frequent in patients with CV disease or peripheral vascular disease. Thus VA thrombosis could probably represent a marker of the severity of the vascular state of these patients.

Limitations of the study

This study is a *post hoc* analysis of a randomized trial and the association observed between AVF thrombosis and survival may potentially be the result of residual confounding. However, all analyses were adjusted on validated predictors of mortality in dialysis. Importantly, we did not adjust for variables collected during follow-up, which could have decreased the association between VA failure and outcome. However, the objective of our analysis was risk stratification rather than causal inference. VA failure seemingly represents a marker of higher risk of death as a result of other factors occurring during the follow-up. Nonetheless, since it is an integrative marker of poor outcome, directing some attention to the occurrence of VA failure remains clinically relevant.

Lastly, given the moderate size of the AVG group, the non-significant association between VA complications and outcomes observed in this group may be due to a lack of statistical power.

Clinical implications and perspectives

This study points to the strong association between AVF thrombosis and patient survival in dialysis. Even in the absence of additional evidence, clinicians should be cognizant that patients with AVF thrombosis have immediate and midterm increased mortality. VA failure could hence serve as an integrative short and midterm risk stratifier in HD patients.

Given that rapid access restoration is seemingly associated with a milder increase in subsequent mortality, clinicians should be aware of the possible role of urgent revascularization. This result could help in prioritizing VA restoration in vascular surgery departments. In addition, as the increase in risk appears to persist after VA thrombosis, these patients may consequently require aggressive general therapeutic interventions in addition to their urgent revascularization. Underlying conditions potentially responsible for VA failure should also be investigated and eventually corrected. An accurate coagulation assessment may be required as well as close monitoring of nutritional and inflammatory status. Finally, targeting the risk factors of uraemic vasculopathy may also be beneficial in preventing VA complications [22].

Careful medical follow-up and multidisciplinary management after the occurrence of thrombosis could be crucial to reduce VA thrombosis rates and associated mortality in this population of patients.

CONCLUSION

AVF/AVG thrombosis is strongly associated with increased all-cause and CV mortality in patients on maintenance HD, especially in the first 90 days after the event and when access is restored >7 days after thrombosis. Consequently, clinicians should pay particular attention to the timing of VA restoration as well as the management of these patients following VA restoration. In all instances, AVF thrombosis should be considered as a major clinical event. The clinical relevance of targeting overall patient risk with more aggressive treatment after VA restoration warrants further exploration in dedicated trials.

SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

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CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

1. Sidawy AN, Spergel LM, Besarab A *et al.* The Society for Vascular Surgery: clinical practice guidelines for the surgical placement and maintenance of arteriovenous hemodialysis access. *J Vasc Surg* 2008; 48(5 Suppl): 2S–25S
2. Vascular Access 2006 Work Group. Clinical practice guidelines for vascular access. *Am J Kidney Dis* 2006; 48(Suppl 1): S176–S247
3. Jindal K, Chan CT, Deziel C *et al.* Hemodialysis clinical practice guidelines for the Canadian Society of Nephrology. *J Am Soc Nephrol* 2006; 17(3 Suppl 1): S1–S27
4. Ethier J, Mendelssohn DC, Elder SJ *et al.* Vascular access use and outcomes: an international perspective from the Dialysis Outcomes and Practice Patterns Study. *Nephrol Dial Transplant* 2008; 23: 3219–3226
5. Roy-Chaudhury P, Sukhatme VP, Cheung AK. Hemodialysis vascular access dysfunction: a cellular and molecular viewpoint. *J Am Soc Nephrol* 2006; 17: 1112–1127
6. Lutz J, Menke J, Sollinger D *et al.* Haemostasis in chronic kidney disease. *Nephrol Dial Transplant* 2014; 29: 29–40
7. United States Renal Data System. 2018 *USRDS Annual Data Report: Epidemiology of Kidney Disease in the United States*. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2018
8. Fellstrom B, Zannad F, Schmieder R *et al.* Effect of rosuvastatin on outcomes in chronic haemodialysis patients – design and rationale of the AURORA study. *Curr Control Trials Cardiovasc Med* 2005; 6: 9
9. Fellström BC, Jardine AG, Schmieder RE *et al.* Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. *N Engl J Med* 2009; 360: 1395–1407
10. Fellstrom B, Holdaas H, Jardine AG *et al.* Effect of rosuvastatin on outcomes in chronic haemodialysis patients: baseline data from the AURORA study. *Kidney Blood Press Res* 2007; 30: 314–322

11. Tonelli M, James M, Wiebe N *et al*. Ultrasound monitoring to detect access stenosis in hemodialysis patients: a systematic review. *Am J Kidney Dis* 2008; 51: 630–640
12. Bradbury BD, Chen F, Furniss A *et al*. Conversion of vascular access type among incident hemodialysis patients: description and association with mortality. *Am J Kidney Dis* 2009; 53: 804–814
13. Allon M, Daugirdas J, Depner TA *et al*. Effect of change in vascular access on patient mortality in hemodialysis patients. *Am J Kidney Dis* 2006; 47: 469–477
14. Bowdle A. Vascular complications of central venous catheter placement: evidence-based methods for prevention and treatment. *J Cardiothorac Vasc Anesth* 2014; 28: 358–368
15. Beathard GA, Litchfield T. Effectiveness and safety of dialysis vascular access procedures performed by interventional nephrologists. *Kidney Int* 2004; 66: 1622–1632
16. Sacks D, McClenny TE, Cardella JF *et al*. Society of Interventional Radiology clinical practice guidelines. *J Vasc Interv Radiol* 2003; 14(9 Pt 2): S199–S202
17. Polkinghorne KR, McDonald SP, Atkins RC *et al*. Vascular access and all-cause mortality: a propensity score analysis. *J Am Soc Nephrol* 2004; 15: 477–486
18. Locatelli F, Canaud B. Dialysis adequacy today: a European perspective. *Nephrol Dial Transplant* 2012; 27: 3043–3048
19. Holme I, Fellstrom BC, Jardin AG *et al*. Prognostic model for total mortality in patients with haemodialysis from the Assessments of Survival and Cardiovascular Events (AURORA) study. *J Intern Med* 2012; 271: 463–471
20. Schneider A, Jardine AG, Schneider MP *et al*. Determinants of cardiovascular risk in haemodialysis patients: post hoc analyses of the AURORA study. *Am J Nephrol* 2013; 37: 144–151
21. Rothuizen TC, Wong C, Quax PH *et al*. Arteriovenous access failure: more than just intimal hyperplasia? *Nephrol Dial Transplant* 2013; 28: 1085–1092
22. Viecelli AK, Mori TA, Roy-Chaudhury P *et al*. The pathogenesis of hemodialysis vascular access failure and systemic therapies for its prevention: optimism unfulfilled. *Semin Dial* 2018; 31: 244–257
23. Blacher J, Guerin AP, Pannier B *et al*. Arterial calcifications, arterial stiffness, and cardiovascular risk in end-stage renal disease. *Hypertension* 2001; 38: 938–942
24. London GM, Blacher J, Pannier B *et al*. Arterial wave reflections and survival in end-stage renal failure. *Hypertension* 2001; 38: 434–438
25. Alpers CE, Imrey PB, Hudkins KL *et al*. Histopathology of veins obtained at hemodialysis arteriovenous fistula creation surgery. *J Am Soc Nephrol* 2017; 28: 3076–3088