

REVIEW ARTICLE

Predictors of Patency after Balloon Angioplasty in Hemodialysis Fistulas: A Systematic Review

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ABSTRACT

Percutaneous transluminal angioplasty (PTA) is an established treatment for dysfunctional hemodialysis fistulas. This article systematically reviews evidence for predictors of patency after PTA. Outcomes assessed were primary, assisted primary, and secondary patency after intervention, and findings were summarized descriptively. This review included 11 nonrandomized observational studies of 965 fistulas in 939 patients. Follow-up ranged from 0 days to 10 years. Study quality was overall suboptimal. Newer fistulas and longer lesion length may be associated with primary patency loss after PTA. Further studies are needed to confirm these findings, to identify potentially modifiable factors, and to guide the testing of new endovascular devices.

ABBREVIATIONS

AVF = arteriovenous fistula, HbA_{1c} = glycosylated hemoglobin, HR = hazard ratio, RR = relative risk

One of the greatest challenges of hemodialysis is the limited durability of vascular access. Access-related complications are a common cause of hospital admission in patients undergoing hemodialysis (1). In the United States, the cost of managing access dysfunction is

approximately \$2.9 billion—15% of the total cost of hemodialysis care (2).

Neointimal hyperplasia is the most common cause of access dysfunction in both autogenous (native arteriovenous fistulas [AVFs]) and nonautogenous (prosthetic grafts) arteriovenous access (3). In native AVFs, although perianastomotic stenosis is most common, neointimal hyperplasia often occurs through the access circuit, particularly at the cephalic arch (4). Percutaneous transluminal angioplasty (PTA) is an established treatment for stenosis in both native AVFs and prosthetic grafts, but patency after angioplasty is highly variable. Only 26%–58% of native AVFs remain functional without subsequent interventions at 12 months (5,6).

Patency in native AVFs after angioplasty depends on a range of clinical, anatomic, and biochemical factors (5,7–9). This review systematically summarizes evidence regarding which risk factors are associated with patency loss in native AVFs after angioplasty.

MATERIALS AND METHODS

Protocol and Focus

This systematic review is reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (10). The review focuses on studies that assessed predictors of patency after balloon angioplasty to maintain native AVF function.

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Search Criteria

A literature search was conducted of publications available up to May 1, 2013, by one investigator. MEDLINE was searched via OvidSP, using the following terms: “renal dialysis,” “renal replacement therapy,” and “arteriovenous shunt, surgical” and “angioplasty” or “endovascular procedures” or “vascular patency.” Reference lists of relevant studies were searched by hand to identify additional publications. One investigator screened the titles and abstracts of all retrieved citations, and the full text of potential studies were reviewed where necessary.

Eligibility Criteria

Studies that assessed predictors of patency in native AVFs after PTA were included. Potential predictors of patency were related to clinical, anatomic, biochemical, or medication factors. Three patency outcomes were used in accordance with the Society of Interventional Radiology (SIR) reporting standards (11). Primary patency after intervention was defined as the interval after PTA until repeated percutaneous intervention or fistula thrombosis. Assisted primary patency after intervention was defined as the interval after PTA until fistula thrombosis or surgical intervention that excludes the treated lesion from the access circuit. Secondary patency after intervention was defined as the interval after PTA until the fistula was surgically declotted, revised, or abandoned.

There were no restrictions on the study size, design, or language. Studies that separated outcomes for native AVFs and prosthetic grafts in statistical analysis were included. We included all relevant publications arising from observational cohort studies. We included studies that combined both immature and mature AVFs in their analyses. We excluded studies focusing solely on balloon-assisted maturation, defined as angioplasty of native fistulas that had not been used for dialysis. We also excluded studies focusing exclusively on percutaneous thrombolysis or thrombectomy, studies focusing on other access types, studies combining endovascular and open surgical repair, studies using patency definitions different from the SIR reporting standards, or studies comparing different devices or techniques.

Data Extraction and Analysis

One investigator used a standardized data sheet to extract data from included studies. Data were extracted for total number of patients and fistulas, fistula location, study design, inclusion of immature or thrombosed fistulas, predictors of patency after intervention, and follow-up duration. Any uncertainty was resolved through consensus discussion with other authors. A meta-analysis pooling the association between individual variables and primary patency after intervention was initially planned; however, data extracted proved unsuitable for meta-analysis.

The reasons for the unsuitability of data are described in the Results section.

Quality Assessment

We developed a modified tool to assess risk of bias in included studies. This assessment tool was based on a validated checklist for nonrandomized studies included in systematic reviews (12) and the SIR reporting guidelines (11). Risk of bias was assessed in seven independent domains: study design (prospective or retrospective), statistical analysis (univariate or multivariate), referral criteria for PTA, complete reporting of all variables to be assessed and results reported, prior AVF interventions described, PTA details adequately described, and description of lesion measurement definitions.

RESULTS

Search Results

Database and reference list searching yielded 2,143 articles, of which full text of 27 articles was examined (Fig). Based on our inclusion and exclusion criteria, we included 13 reports of 11 studies that involved 965 AVFs in 939 patients (Table 1). Follow-up ranged from 0 days to 10 years. All studies were single-center reports with a small number of patients. Only three studies included > 100 participants; the largest study comprised 162 participants (Table 1).

Quality Assessment

The quality of studies was overall suboptimal (Table 2). Of 11 studies, 8 were retrospective in design, and 3 were prospective. No studies reported how complete their data were or were explicit about missing data. Of 11 studies, 5 did not perform multivariate analysis to allow for the combined effects of potential risk factors. These studies used univariate analysis alone, used the log-rank test to compare categorical variables, or did not provide enough information to assess statistical methods adequately. Eight studies did not report whether previous percutaneous interventions had been performed in the AVFs being investigated. In five studies, predictors of patency were selectively reported; for example, nonsignificant variables were not reported, or the study methods did not define a priori which variables would be assessed. Four studies included angioplasties in both immature and mature AVFs. Studies often included patients several times if they had more than one AVF during the study period. Current evidence suggests that AVF surveillance may reduce thrombosis rates (14), but there was considerable variability in the reporting of referral criteria and surveillance protocols. All but one study (comprising 140 participants) converted continuous measures into categories for analysis (9). In some cases, multiple different cutoff points for the same measure were applied in different studies, producing some statistically

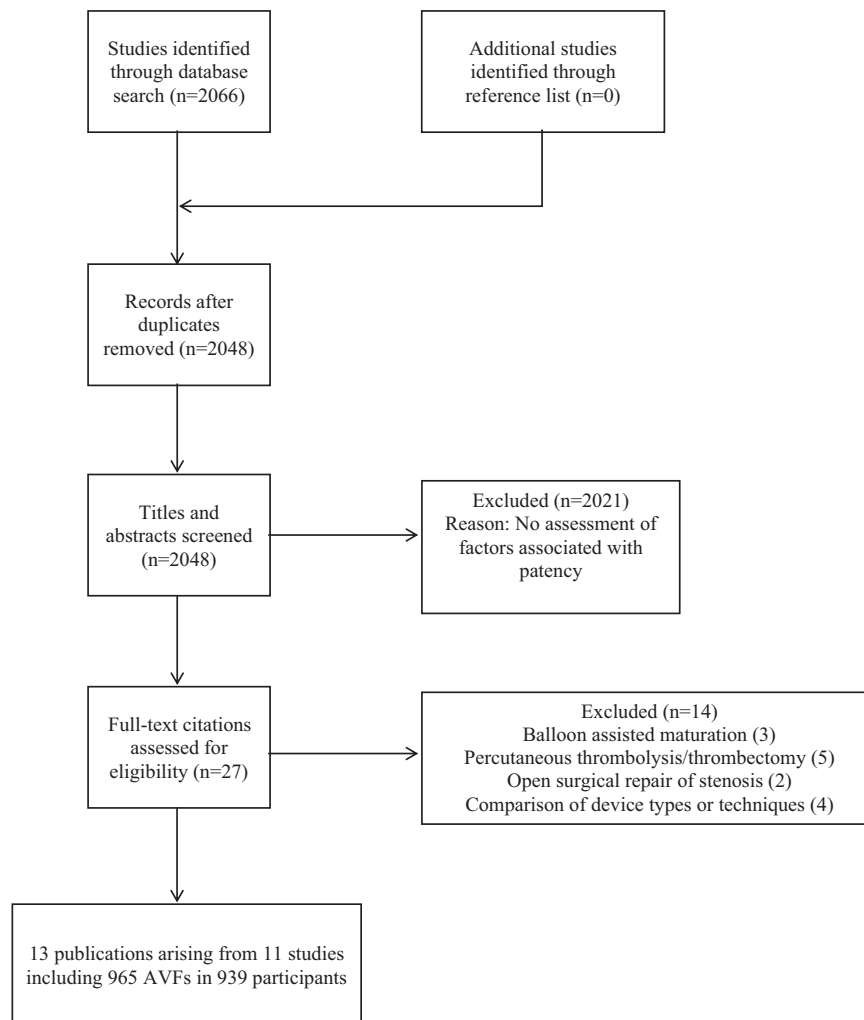


Figure. Flow diagram showing identification of studies for inclusion in a systematic review of factors predicting fistula patency after angioplasty.

significant results. In some cases, essential details, such as AVF location and intervention details, were omitted. For these reasons, we chose to describe our findings descriptively, rather than perform a meta-analysis.

Primary Patency after Intervention

Of 11 studies, 10 assessed the association of various anatomic, clinical, biochemical, and medication factors and primary patency. These studies and their findings are summarized in [Table 3](#).

Various anatomic characteristics were shown to be associated with primary patency. In three of seven studies, it was found that the newer the fistulas were at the time of angioplasty, the shorter the primary patency. In two of these studies, fistula age as a continuous variable was a significant predictor (hazard ratio [HR], 0.97 per month increase, $P = .038$, and HR not reported, $P = .009$) (7,15). One study found that fistulas < 6 months old at angioplasty predicted shorter primary patency compared with fistulas > 6 months old (relative risk [RR], 4.52, $P = .007$) (6). One large study ($N = 151$)

found that upper arm fistulas had shortened primary patency compared with forearm fistulas (HR, 1.81, $P = .005$) (8). Although four other studies did not show an association between fistula location and patency, two of these studies had much smaller sample sizes (5,15). Two studies that focused predominately on radiocephalic fistulas found that longer lesions had shortened primary patency. One study found that lesions > 4 cm predicted primary patency loss (RR, 5.51, $P = .004$) (6), whereas the other found that lesions > 2 cm predicted shorter primary patency (RR, 7.5, $P = .002$) (5). Studies that did not describe fistula location and studies that included a relatively equal proportion of upper arm and forearm fistulas reported no association between lesion length and primary patency. Lesion location, presence of multiple lesions throughout the access circuit, and degree of stenosis before and after angioplasty did not predict primary patency in any of the studies.

In terms of clinical and cardiovascular risk factors, only diabetes was associated with primary patency loss in one study (HR, 1.97, $P = .04$) (9). Seven other studies

Table 1. Summary of Included Studies

Author, Year	No. Patients	No. AVFs	AVF Location	Immature AVFs Included	Thrombosed AVFs Included	Follow-up (mo)
Clark et al, 2002 (5)	65	65	Forearm and upper arm	Yes	Yes	6–26
Doi et al, 2008 (17)	54	54	Not reported	Unclear	Unclear	12
Heerwagen et al, 2012 (15)	61	61	Forearm and upper arm	No	Unclear	0.7–31.1
Heye et al, 2011 (7)	162	167	Forearm and upper arm	Yes	No	36
Liu et al, 2007 (16)	82	82	Forearm and upper arm	No	No	6
Maeda et al, 2005 (6)	59	60	Forearm	No	Yes	0–51
Manninen et al, 2001 (20)	51	53	Forearm	Yes	Yes	0.5–67.1
Mortamais et al, 2013 (18)	75	75	Forearm	Yes	No	1–122
Rajan et al, 2003 (4), 2004 (8)	140	151	Forearm and upper arm	No	No	0.1–119
Sugimoto et al, 2003 (19)	50	57	Forearm	Unclear	Yes	12
Wu et al, 2009 (9), 2010 (13)	140	140	Not reported	No	No	6

AVF = arteriovenous fistula.

Table 2. Quality Assessment

Author, Year	Prospective	Multivariate Analysis	Indications for Referral	Assessed Variables Prespecified*	First Intervention in AVF	Intervention Details Adequate [†]	Lesion Definitions Described [‡]
Clark et al, 2002 (5)	No	Yes	Yes	No	Unknown	Yes	No
Doi et al, 2008 (17)	No	No	No	Yes	Unknown	No	Not applicable
Heerwagen et al, 2012 (15)	Yes	Yes	Yes	No	Yes	Yes	No
Heye et al, 2011 (7)	No	No	Yes	Yes	Yes	Yes	No
Liu et al, 2007 (16)	No	Unclear	No	No	Unknown	No	Not applicable
Maeda et al, 2005 (6)	No	Yes	No	Yes	Unknown	Yes	No
Manninen et al, 2001 (20)	Yes	Yes	Yes	No	Unknown	Yes	No
Mortamais et al, 2013 (18)	No	Unclear	Yes	Yes	Unknown	Yes	No
Rajan et al, 2003 (4), 2004 (8)	No	Yes	Yes	Yes	Unknown	Yes	No
Sugimoto et al, 2003 (19)	No	No	Yes	Yes	Unknown	Yes	No
Wu et al, 2009 (9), 2010 (13)	Yes	Yes	Yes	No	No	Yes	Yes

AVF = arteriovenous fistula.

*Methods clearly state all variables to be assessed, and all variables are reported in results or tables.

[†]Intervention technique and materials adequately described or referenced.

[‡]Definitions of lesion length (in cases of multiple lesions) and percentage stenosis adequately described.

Table 3. Factors Associated with Primary Patency after Intervention

Author, Year	Mean Patient Age (y)	Mean AVF Age (mo)	Male (%)	DM (%)	Upper Arm AVF (%)	Lesion Length Classification (cm)	Other Variables Assessed	Significant Findings and Magnitude of Effect
Heerwagen et al, 2012 (15)	63	20	66	32	40	< 2 vs > 2	Lesion location, multiple lesions, stenosis before and after PTA (%), PVD, vessel disease score*, blood flow after intervention, change in blood flow, previous interventions	AVF age (HR, 0.97 per month increase, $P = .038$); previous interventions (HR, 2.94, $P = .008$)
Heye et al, 2011 (7)	66	19	62	35	58	Linear	Prior AVF, lesion location, multiple lesions, stenosis before and after PTA	AVF age (HR, per month increase not reported, $P = .01$)
Doi et al, 2008 (17)	63	Not assessed	57	37	Not assessed	Not assessed	Calcium channel blocker, antiplatelet, angiotensin receptor blocker	Calcium channel blocker (OR, 5.1, $P < .05$)
Liu et al, 2007 (16)	62	41	39	45	10	Not assessed	Hypertension, total cholesterol, triglycerides, smoking, calcium, phosphate, CPP, PTH, URR, albumin, aspirin	Hypertension (HR not reported); smoking (HR not reported); URR (RR, 1.05, $P = .009$); CPP (RR, 1.22, $P = .042$); albumin (RR, 0.32, $P = .001$)
Maeda et al, 2005 (6)	62	Unreported	75	Unreported	0	< 4 vs > 4	Total occlusion, multiple lesions, balloon diameter, duration of dialysis	Lesion length > 4 cm (RR, 5.21, $P = .004$); AVF age < 6 mo (RR, 4.52, $P = .007$)
Rajan et al, 2004 (8)	62	Unreported	74	30	38	Not assessed	Multiple lesions	Upper arm AVF (HR, 1.81, $P = .005$)
Clark et al, 2002 (5)	64	24	57	42	28	< 2 vs > 2, < 5 vs > 5, < 10 vs > 10	CAD, PVD, vessel disease score*, lesion location, stenosis before and after PTA (%), intervention type	Lesion length > 2 cm (RR, 7.5, $P = .002$); vessel disease score* (RR, 1.6, $P = .03$)
Sugimoto et al, 2003 (19)	67	Unreported	70	Unreported	0	Long vs short segment (not defined)	Multiple lesions, lesion location, total occlusion	None
Manninen et al, 2001 (20)	59	10.5	57	Not assessed	100	Linear	Lesion location, multiple lesions, intervention type	None
Wu et al, 2009 (9)	61	Unreported	42	35	Unreported	Linear	Hypertension, smoking, lesion location, reference vessel diameter, stenosis before and after PTA (%), metabolic markers [†] , inflammatory markers [‡] , creatinine, Kt/V , homocysteine, ADMA, medications [§]	ADMA (HR, 2.65, $P = .005$); DM (HR, 1.97, $P = .04$); LDL (HR, 2.29, $P = .03$); HbA_{1c} > 7% (log-rank, $P = .01$) (13)

ADMA = asymmetric dimethylarginine; AVF = arteriovenous fistula; CAD = coronary artery disease; CPP = calcium phosphate product; DM = diabetes mellitus; HbA_{1c} = glycosylated hemoglobin; HR = hazard ratio; Kt/V = measure of dialysis adequacy; LDL = low-density lipoprotein; OR = odds ratio; PTA = percutaneous transluminal angioplasty; PTH = parathyroid hormone; PVD = peripheral vascular disease; RR = relative risk; URR = urea reduction ratio.

*Composite variable of DM, CAD, and PVD.

[†]LDL, high-density lipoprotein, triglycerides, calcium, phosphate, albumin, and hemoglobin.

[‡]High-sensitivity C-reactive protein, interleukin-1 β , interleukin-6, tumor necrosis factor- α , monocyte chemoattractant protein-1, E-selectin, P-selectin, intercellular adhesion molecule-1, and vascular adhesion molecule-1.

[§]Antiplatelets, nitrates, beta blockers, calcium channel blockers, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, lipid-lowering agent.

with longer follow-up found no association between diabetes in primary patency loss. One study found that a composite of diabetes, coronary artery disease, and peripheral vascular disease was associated with shorter primary patency if more than one comorbidity was present (RR, 1.6, $P = .03$) (5). History of coronary artery disease or peripheral artery disease did not predict primary patency in two studies. Patient age and gender did not affect primary patency in any of the studies.

Two studies assessed the association between metabolic and inflammatory markers and primary patency. One study showed that increased asymmetric dimethylarginine and low-density lipoprotein significantly increased the risk of primary patency loss (HR, 2.65, $P = .005$, and HR, 2.29, $P = .03$, respectively) (9). In another publication from the same study, glycosylated hemoglobin (HbA_{1c}) $> 7\%$ was associated with shorter primary patency compared with $HbA_{1c} < 7\%$ (log-rank, $P = .01$) (13). Another study found that low albumin and increased calcium phosphate product were associated with shorter primary patency (RR, 0.32, $P = .001$, and RR, 1.22, $P = .042$, respectively) (16). One study investigated the association between various inflammatory markers and primary patency (Table 3) (9,13). None of the markers were associated with primary patency.

Two studies assessed the association between medications and primary patency. One small study ($N = 54$) found that calcium channel blockers improved patency at 12 months (odds ratio, 5.1, $P < .05$) (17).

Assisted Primary Patency after Intervention

Two studies assessed predictors of assisted primary patency (Table 4). One study found that residual

stenosis $> 50\%$ after angioplasty was associated with shorter assisted primary patency (RR, 2.92, $P = .039$) (18). In the other study, patient age > 75 years predicted shorter assisted primary patency compared with patient age 65–75 years (log-rank, $P = .011$) (7).

Secondary Patency after Intervention

Three studies assessed predictors of secondary patency (Table 4). Increased patient age was associated with secondary patency loss in two studies. Patient age > 70 years shortened secondary patency in one study (log-rank, $P = .029$) (19). Patient age > 75 years was associated with shorter secondary patency in another study (log-rank, $P = .014$) (11). In the same study, fistulas < 6 months old at angioplasty were associated with shorter secondary patency compared with fistulas 6–12 months old and fistulas > 12 months old (log-rank, $P = .037$ and $P = .005$, respectively). Two other studies found no association between fistula age and secondary patency (8,19).

DISCUSSION

Our findings suggest that fistula and lesion characteristics, such as newer fistulas and longer lesion length, may be associated with primary patency loss after balloon angioplasty. This association suggests that hemodynamic shear stress and anatomic factors are the most important determinants of restenosis (3). There are fewer studies that assess the predictors of assisted primary and secondary patency; however, increased patient age appears to be important and is possibly a reflection of the quality of the peripheral vasculature.

Table 4. Factors Associated with Assisted Primary and Secondary Patency after Intervention

Author, Year	Variables Assessed	Outcome	Significant Variables	Effect Magnitude
Mortamais et al, 2013 (18)	Patient age, gender, DM, RC AVF position, AVF age, immature AVF, lesion length and location, stenosis before and after angioplasty (%)	Assisted primary patency	Residual stenosis $> 50\%$ after angioplasty	RR, 2.92, $P = .04$
Heye et al, 2011 (7)	Patient age, gender, AVF age and location, prior AVF, DM, lesion characteristics	Assisted primary patency and secondary patency	Assisted primary patency Patient age > 75 y (vs 65–75 y) Secondary patency Patient age > 75 y (vs 65–75 y) AVF age < 6 mo (vs 6–12 mo and > 1 y)	Not reported, $P = .01$ Not reported, $P = .01$ Not reported, $P = .04$ and $P = .005$
Rajan et al, 2004 (8)	Patient age, gender, AVF age and location, DM, multiple lesions	Secondary patency	None	Not applicable
Sugimoto et al, 2003 (19)	Patient age, gender, AVF age and location, DM, multiple lesions	Secondary patency	Patient age > 70 y	Log-rank, $P = .03$

AVF = arteriovenous fistula; DM = diabetes mellitus; RC = radiocephalic; RR = relative risk.

Fistulas in which stenosis develops early after creation are likely to be intrinsically faulty. Early dysfunction may result from a diseased vein with preexisting pathology or from a previously healthy vein that exhibits accelerated neointimal hyperplasia in response to AVF creation. In the latter case, it is unsurprising that restenosis occurs sooner compared with AVFs that take longer for stenosis to develop. The HR for the effect of fistula age as a continuous measure was less powerful (15), suggesting that the highest risk of reintervention is in fistulas requiring angioplasty within 6 months of creation. Higher flow rates and turbulent flow are likely to explain observed shorter primary patency in upper arm compared with forearm fistulas in one large study (8).

Longer lesions were associated with shorter primary patency after angioplasty in two studies with significant cutoff values of 2 cm and 4 cm (5,6). However, lesion length was defined variably among studies, especially in the presence of multiple lesions; either lesion length was excluded (5), or longest and cumulative length was reported (6,20). It is possible that lesion length is important in more peripheral lesions (eg, juxtaanastomotic stenosis) but less influential in central lesions (eg, cephalic arch stenosis), where extrinsic clavicopectoral fascia compression and the presence of valves may limit vascular remodeling (21).

Although juxtaanastomotic and cephalic arch stenoses are especially problematic (21,22), this review does not provide any insights into the association between lesion location and patency. Six studies analyzed lesion location as a dichotomous variable, but classification of lesion location was different in each. Examples include cephalic arch versus other (15), anastomosis versus other (20), upper arm versus forearm (9), and juxtaanastomotic versus central veins (5). None of these were significant, and so it is difficult to surmise the effect of lesion location on patency.

Degree of stenosis before angioplasty was not associated with patency outcomes in any study. This result is probably due to the fact that the conventional definition of stenosis expressed as a percentage is inaccurate in the venous circuit because the adjacent vein may be small, dilated after stenosis, or aneurysmal. Large differences in degree of stenosis can be calculated depending on which venous segment is used as a reference point (23).

Most studies found that diabetes was not associated with patency after angioplasty. However, a previous review of fistula patency (beginning from surgical creation) concluded that diabetes was an important risk factor for fistula dysfunction (24). Metabolic alterations associated with diabetes may cause a prothrombotic environment, endothelial dysfunction, and dysregulation of growth factor, all predisposing to restenosis (13). Whether this explanation is applicable to both the arterial and the venous systems is unclear.

Although $HbA_{1c} > 7\%$ was associated with restenosis within 6 months in one study (13), this observation was

based on log-rank test alone. HbA_{1c} is an inaccurate tool for accessing glycemic control in patients undergoing hemodialysis owing to anemia, blood loss during dialysis, reduced erythrocyte life span, and variable erythropoietin doses (25).

Systemic inflammation is likely to be less important than hemodynamic factors in determining restenosis after angioplasty. Although others have found that baseline C-reactive protein predicts thrombosis events in fistulas and grafts (26), two relatively large prospective studies in this review found no association between various inflammatory markers (Table 3) and primary patency after intervention at 6 months.

Although there was some evidence for associations between metabolic markers and primary patency after angioplasty, their importance is unclear. Plasma asymmetric dimethylarginine has been implicated in endothelial dysfunction (27) and was shown to predict fistula restenosis (9), but more studies are required. Venous neointimal hyperplasia lacks lipid-laden foam cells and other characteristics of arterial atherosclerosis, and the association between low-density lipoprotein and primary patency loss should not be interpreted as a causal relationship.

Calcium channel blocker use was associated with improved primary patency in one small study with significant risk of bias. This finding was in contrast to the largest study of medication use in patients undergoing dialysis, the Dialysis Outcomes and Practice Patterns Study, which found no association between medication use and unassisted fistula patency (28). Angiotensin-converting enzyme inhibitors were the only medication found to be associated with prolonged cumulative fistula patency.

Our review was limited by bias in the design and reporting of the studies we examined, and this precluded formal data synthesis with meta-analysis. Despite this limitation, we were able to describe explicitly potential biases we found when appraising studies, permitting readers to interpret our findings in the light of these potential biases. Potential studies may have been missed by our search strategy, which used only one database. One reviewer performed the search and extracted data, providing another source of potential error. Nevertheless, our summary presents the best current evidence that exists to answer our research question.

Our review highlights the contentious and contradictory evidence for risk factors for patency loss after angioplasty, which is based largely on retrospective data. There is a need for multicenter, prospective observational studies, possibly in the form of a registry, to identify a set of predictors with an emphasis on modifiable factors, such as the use of angiotensin-converting enzyme inhibitors, to extend AVF patency after PTA. Identifying predictors of patency after PTA can also guide the testing and application of new endovascular technology, such as cutting balloons (29), drug-eluting balloons (30), and stent grafts (31).

In conclusion, current evidence suggests that newer fistulas and longer lesions may be associated with reduced primary patency after angioplasty. These findings are based on small observational studies of sub-optimal quality. More large, well-designed, and well-reported studies are needed to confirm these findings and to guide the testing of new endovascular devices and surgical techniques in randomized trials.

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