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Preferred haemodialysis vascular access for diabetic chronic kidney disease patients: a systematic literature review

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ABSTRACT

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INTRODUCTION

The incidence and prevalence end-stage kidney disease (ESKD) has been growing over the last decade by 4-8% per annum worldwide, with diabetes mellitus (DM) as one of the leading causes (1). In parallel, the number of surgical and interventional procedures required to establish and maintain the arteriovenous vascular access for haemodialysis (HD) keeps rising every year (2). Despite many efforts, many patients are still dialyzed on a permanent tunneled catheter (PTC), although there is considerable geographic variation. DOPPS I data indicate that in Europe, HD patients were 3-fold more likely to have an autogenous arteriovenous fistula (AVF) as compared to North America. However, between DOPPS I and III, AVF use increased to 47% in the United States and decreased slightly from 80% to 74% in Europe (3). Actually, the proportion of prevalent HD patients with permanent catheters in Europe has been estimated to be as high as 25% (4). The increase of comorbidities such as DM (from 18% to 33%), and vascular disease (from 22% to 34%) in HD patients between DOPPS I and III probably led to higher proportions of patients at risk for unsuccessful AVF creation.

In an effort to improve vascular access outcomes, the National Kidney Foundation and the European Renal Association/European Dialysis and Transplant Association published guidelines for vascular access (5, 6). Based on these recommendations, a special project was launched in the United States, known as the Fistula First Breakthrough Initiative (7). The purpose of this initiative was to increase the likelihood that every patient would receive an autogenous vascular access. The Work Group however recognized after a while that in some cases, the “fistula first at all costs” approach leads to non-maturation and access failure despite repetitive interventions in certain subgroups, including diabetics, elderly and those with peripheral vascular disease (3, 4). Therefore, it is uncertain whether attempting to create a fistula first in these high risk patients is the most cost-effective or optimal solution for each individual.

With this background in mind, we performed a systematic review of the available evidence to clarify what is the most advisable strategy of vascular access planning in diabetic ESKD patients (with respect to type -catheter, autogenous fistula or graft- and position) in terms of impact on patient- and technique-centered outcomes.

METHODS

Data source and search strategy

MEDLINE, EMBASE and CENTRAL databases were searched for English-language articles without time restriction through focused, high sensitive search strategies (**Supplementary Table 1**). References from relevant studies and reviews published on the same topic were screened for supplementary articles.

Study selection

We included any study providing outcome data on diabetics on chronic haemodialysis treatment on the basis of the type of vascular access primarily attempted. Studies were considered without restrictions of duration of follow-up. Diabetes (type I or II) was considered when it was either a cause of end-stage renal disease or a superimposed condition. We considered any possible type of vascular access, including: tunnelled catheters placed in any position (Jugular vein, Femoral vein, Subclavian vein), grafts placed in any position (Radial artery, Brachial artery) or autogenous fistulas placed in any position (Radial artery, Brachial artery). Outcomes of interest were: vascular access patency, vascular access infections, all cause- and cardiovascular-mortality. Studies were excluded if: 1) not dealing with diabetics; 2) not providing the above mentioned outcome data in relationship to the type of first placed vascular access; 3) dealing with vascular accesses not related to haemodialysis. Case reports, reviews, editorials, letters

and studies performed on children (age<18) or animals were excluded as well, although screened as potential sources of additional references. Selection of relevant studies were independently performed by two Authors (DB and LC). Discrepancies were solved collegially by discussion amongst DB and LC.

Quality assessment

We used the Newcastle-Ottawa Scale to assess the study quality for observational studies. This scale considers a quality score calculated on the basis of three major items: Study participants (0 to 4 points), adjustment for confounding (0 to 2 points) or ascertainment of the exposure or outcome of interest (0 to 3 points) with a maximum score of 9 points which represents the highest methodological quality.

Data extraction and analysis

Data extraction and analysis were performed by two reviewers independently (DB and LC). In studies considering mixed populations, the subgroup of patients with documented diabetes was selectively described only if corresponding data were available.

RESULTS

Search results

The flow diagram of the selection process is depicted in **Figure 1**. Two hundred and sixty-two potentially relevant references were initially found. A total of 213 citations were excluded after title/abstract skimming because they were clearly not pertinent for the topic of our review or because of search overlap. Amongst the 49 studies selected for full text examination, 36 studies were excluded because of the following: dealing

with an inappropriate population/problem (n=16), dealing with an inappropriate intervention (n=4) or not including a proper comparator (n=13), no outcome data available (n=3). A total of 13 studies were therefore reviewed in detail and included in the review. Main characteristics of these studies are summarized in **Table 1**.

Study characteristics

Amongst the thirteen studies reviewed, two were prospective cohort studies (8, 9), ten were retrospective cohort studies (10-19) and one was a case-control study (20). The number of patients ranged from 127 (15) to 5198 (12). Diabetes was present in 22 (8) to 55% (20) of the study populations. Follow up duration ranged from 24 (11) to 80 (12) months. The overall study quality was low to moderate.

Ravani *et al.* (8) analyzed a cohort of 197 incident HD patients (22% DM) who underwent distal and proximal AVF creation by nephrologists in a single-centre. At the start of HD therapy, 117 patients (59.7%) had a dialysis catheter and the remaining patients had an AVF. Saxena *et al.* (9) analyzed the vascular access-related sepsis and mortality among 218 HD patients (29% DM) with different types of vascular access (AVF, AVG, temporary and permanent dialysis catheters). In the study of Chan *et al.* (10), a cohort of 764 incident HD patients with >65 years old (43% DM) who underwent AVF and AVG creation were studied. Patients with dialysis catheters were excluded. David *et al.* (11), analyzed the vascular access patency in a cohort of 274 chronic kidney disease patients (26% DM) referring to AVF creation at several locations (distal, middle-arm and proximal AVF). Dhingra *et al.* (12) analyzed the all-cause, cardiovascular and infection-related mortality among a cohort of 5189 HD patients (31% DM) with AVF, AVG and dialysis catheters. Diehm *et al.* (13) analyzed the vascular access patency on a cohort of 244 HD patients (25% DM) with different

types of vascular access (AVF, AVG and dialysis catheters). In the study of Field *et al.* (14), a cohort of 289 incident HD patients (36% DM) who underwent distal and proximal AVF creation was studied. Hammes *et al.* (15) analyzed a cohort of 127 incident HD patients (41% DM) who underwent AVF angiography aiming to determine the time to the development of clinically significant stenosis among patients with and without cephalic arch lesions. Konner *et al.* (16) analyzed the vascular access patency and patient survival in a cohort of 247 chronic kidney disease patients (23% DM) who underwent distal or proximal AVF creation in a single-center. In a later study of Konner *et al.* (17), the authors analyzed the primary and cumulative patency rates in a cohort of 748 chronic kidney disease patients (24% DM) who underwent either distal, proximal perforating or non-perforating vein AVF creation in a single center. Murphy *et al.* (18), analyzed a cohort of 293 chronic kidney disease patients (23% DM) who underwent proximal AVF creation in a single center, comparing <65 and >65 year-old, and male *versus* female patients. Leapman *et al.* (19) analyzed a cohort of 150 chronic kidney disease patients (34% DM) who underwent wrist AVF creation, aiming to determine the cumulative patency of the vascular access. In the study of Yeager *et al.* (20), a population of 222 HD patients (54% DM) was analyzed. Patient survival was determined among those with finger gangrene and those without it.

Study Outcomes

Mortality

Dhingra *et al.* (13) reported a higher all-cause, infection-related and cardiovascular-related mortality among patients with a dialysis catheter, in comparison to those with an AVF (RR=1.54, p<0.002). Also, all-cause and infection-related mortality was significantly higher among those with an AVG *versus* AVF (RR=1.41, p<0.003). On the

other hand, in the study of Chan *et al.* (10), mortality was not significantly higher in patients with an AVG compared to those with an AVF (RR=1.34, p=0.123). Finally, Konner (16) described a higher mortality rate among DM patients with an AVF versus non-DM patients (70% versus 40% at 60 months follow-up, respectively).

Vascular access patency

Ravani *et al.* (8), Diehm *et al.* (13) and Konner (16) reported lower patency rates of AVF among DM *versus* non-DM patients (HR 2.38, p=0.04; OR 0.4, 95% CI 0.2-0.7, respectively). On the other hand, Murphy *et al.* (18) and Field *et al.* (14) reported similar AVF patency rates between DM and non-DM patients (approximately 40% and 30%, respectively; no effect measure reported). Within the DM group, both Ravani *et al.* (8) and Konner (16) reported similar secondary patency rates among those with distal *versus* proximal AVF and Murphy *et al.* (18) reported similar cumulative patency rates between young and older patients. On the other hand, Field *et al.* (14) reported a higher patency rate for DM patients with a proximal *versus* distal AVF and Murphy *et al.* (18) reported a higher patency rate in male *versus* female DM patients. In these studies, comparisons within the DM population were entirely descriptive. In another study, Konner *et al.* (17), reported a lower primary patency rate in patients with non-perforating proximal AVF *versus* perforating proximal AVF and distal AVF (approximately 50%, 80% and >80%, respectively); the cumulative patency rates among the three study groups was similar (approximately 90%, 80% and 80%, respectively) and the thrombosis rate was lower among those with a proximal perforating AVF (6.3, 3.0 and 0.8 per 100 patients-at risk; no effect measure reported). In the study of Chan *et al.* (10), the authors reported similar vascular access patency rates between patients with an AVF and an AVG (60 *versus* 50%, OR=1.49, p=0.244).

David *et al.* (11) described similar patency rates between distal, middle-arm and proximal AVF (57%, 55% and 30%, respectively). Hammes *et al.* (15) reported that the presence of cephalic arch stenosis in DM patients with an AVF was not a risk factor for the development of a subsequent stenosis. Finally, Yeager *et al.* (20), reported that DM and premature atherosclerotic disease were independent risk factors for finger gangrene.

Vascular access-related infections

The study of Saxena *et al.* (9), showed that vascular access-related sepsis was significantly lower among patients with an AVF (8.3%) in comparison with those with an AVG (33.3%) or a permanent dialysis catheter (27.3%) (AVG *vs.* AVF, RR=4.02, $p<0.0006$; permanent catheter *vs.* AVF, RR=3.29, $p<0.03$). Patients with temporary femoral catheters presented the highest sepsis-related mortality (100%, RR=5.78, 95%CI 1.55-21.54). Dhingra *et al.* (13), reported a higher vascular access-related infection associated mortality among DM patients with permanent catheters and AVGs, in comparison with those with AVFs (RR=2.30, $p=0.06$; RR=2.47, $p=0.02$; respectively).

DISCUSSION

In our systematic review, including 13 studies comprising over 2800 participants with DM, we found that DM patients using a dialysis catheter apparently experience a higher risk of death and infection compared with patients who successfully achieved and maintained an AVF as HD access. Primary patency rates appeared to be lower in diabetics *versus* non-diabetics. The comparison between the use of an AVG or an AVF as HD access generated conflicting results.

The preference of AVF over all other forms of access arises from their functional advantages because of a lower rate of complications. Autogenous fistulae have lower rates of infections than catheters and AVGs, and the lowest rate of thrombosis, providing longer survival of the access (5, 6). Perl *et al.* (21) reported that patients starting HD using a central venous catheter had a higher risk of death in the first year compared to those who started HD with an AVF or AVG. Ravani *et al.* (22) performed a systematic review aiming to quantify the associations between vascular access type and mortality, infection, and cardiovascular events. The authors showed that persons using central venous catheters for HD experience a much higher risk of death, infection, cardiovascular events, and hospitalization compared with persons who achieve an AVF or an AVG as HD access. However, AVG use was also associated with increased risk of death, infection, and hospitalization, compared to the use of an AVF. Nevertheless, since most of the data on this field was obtained from observational studies, there is always the reservation that adjustment for baseline comorbidity cannot be complete. As a consequence, the presence of a functioning AVF is probably a marker of a patient's health and adherence, and so all or even most of the superior outcome may not be related to the AVF itself but rather to selection bias (23). On the contrary, catheter use is associated with acute illness and late presentation for dialysis, factors that are associated with high mortality and that may be difficult to adjust for. Dhingra *et al.* (13) reported a lower survival among those patients using an AVG and Chan *et al.* (10) reported similar outcomes between ESRD patients achieving an AVF or an AVG. However, the study populations on these two studies were quite different - Dhingra *et al.* (13) included HD patients > 15 years old and Chan *et al.* (10) included only HD patients > 65 years old. Although overall ESKD diabetic patients probably do better with an AVF, in comparison with a dialysis catheter or an AVG, diabetic patients aged

65 years and older probably may experience similar outcomes either with an AVF or graft.

Our review suggests that diabetic patients have a decreased odds for vascular access long-term survival, often resulting in repetitive interventions. There is no sufficient data to allow meaningful comparison of different techniques and locations on the arm (wrist/forearm/elbow), and existing data are conflictive. It is likely that this is just a reflection of different case-mix, bias by indication and experience of involved surgeons. It seems obvious in the light of good surgical practice that when planning permanent access placement, one should always consider the most distal site possible because it preserves more proximal vessels and it has fewer complications (5). However, the major disadvantage of distal AVF is the relatively high primary failure rate. In view of the more limited life expectancy, a primary choice for more proximal places can be discussed, especially in the elderly and in those with additional comorbidities. In this regard, vascular mapping in preparation for the creation of a vascular access should be performed in all patients in order to maximize the chance of AVF placement success (5, 6).

Our review has some strengths and limitations that deserve mentioning. Strengths include that we performed a systematic search of medical databases, and that data extraction and analysis were made by two independent reviewers according to current methodological standards. However, although comprehensive search strategies were implemented, publication bias cannot be excluded. In order to maximize the number of included studies we decided to adopt broad criteria, considering any paper including at least a subpopulation of HD patients with acknowledged DM and outcome data available according to the first type of vascular access placed. Yet, in most studies diabetics often represented only a minor subpopulation of the whole study cohort. This

may therefore hamper the generalizability of findings to the whole diabetic HD population. There was a high heterogeneity among studies with respect to the study design, number of subjects enrolled, severity and vintage of diabetes, presence of co-morbidities and, above all, age, which prevented us to perform data pooling. Furthermore, all the studies had an observational design (mostly retrospective) and we were unable to find even a single randomized trial providing useful data for our review purpose. Also of note, data on the rates of vascular access patency were often only descriptive. This, again, makes it highly challenging to draw even a preliminary conclusion on what is the optimal vascular access for HD to be universally recommended in diabetics.

In conclusion, although it is widely recognized that an AVF appears to be the access of choice for younger and healthier HD diabetic patients, the everlasting question concerning older, sicker patients with risk factors for AVF failure and associated complications still remains unresolved. Patients should be well informed on the available evidence on vascular access. A strategy whereby reasonable effort is done to create an autogenous vascular access in those with good prognosis, both with regard to primary patency as to life expectancy, seems to be a defensible approach based on the available evidence. Much more clinical investigations in this important field are urgently needed, in view of the importance for this increasing patient group.

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Declaration of Interest

None of the Authors reports a conflict of interest with regard to issues dealt with in this systematic review. The declarations of interest of interest of the different authors can be found online at www.european-renal-best-practice.org

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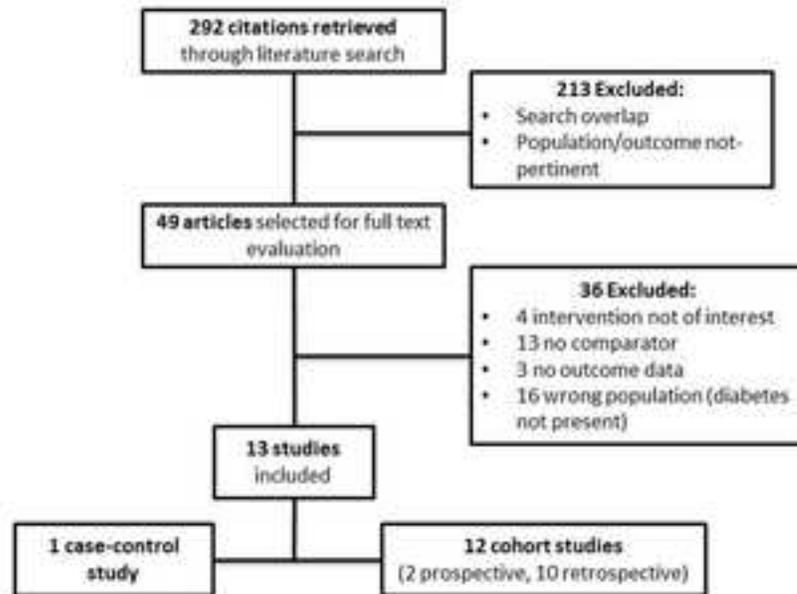
Table I. Summary of studies included in this review

Author	Year	Study type	Population	Follow up	Vascular access	Outcome(s)	Results
Chan et al.	2007	Retrospective multicentre cohort study	Prevalent haemodialysis patients	25 months	AVF AVG	<u>Patient survival</u> AVF vs. AVG <u>Survival of the technique</u> AVF vs. AVG	60% vs. 50% (~) OR=1.34 (p=0.123) 60% vs. 50% (~) OR=1.49 (p=0.244)
David et al.	2010	Retrospective single-centre cohort study	Incident haemodialysis patients	80 months	Distal AVF Middle-arm AVF Proximal AVF	<u>Survival of the technique</u> Distal AVF Middle-arm AVF Proximal AVF	57% (*) 55% 30%
Dhingra et al.	2001	Retrospective multicentre cohort study	Haemodialysis patients	2 years	AVF AVG CVC	<u>Patient survival</u> CVC vs. AVF AVG vs. AVF <u>Vascular access-related infection associated mortality:</u> CVC vs. AVF AVG vs. AVF	60% vs. 70% (~) RR=1.54 (p<0.002) 65% vs. 70% (~) RR=1.41 (p<0.003) RR=2.30 (p=0.06) RR=2.47 (p=0.02)
Diehm et al.	2010	Retrospective single-centre cohort study	Chronic kidney disease patients	2 years	AVF AVG CVC	<u>Survival of the technique</u> DM vs. non-DM	Primary patency rate OR 0.6 (95% CI 0.3-1.0) Secondary patency rate OR 0.4 (95% CI 0.2-0.7)
Field et al.	2008	Retrospective single-centre cohort study	Incident haemodialysis patients		Distal AVF Proximal AVF	<u>Survival of the technique</u> DM vs. non-DM DM	34% vs. 26% (p=0.11) Better survival of proximal

							vs. distal AVFs (*)
Hammes et al.	2008	Retrospective single-centre cohort study	Incident haemodialysis patients who underwent fistulae angiography	78 months	AVF	<u>Survival of the technique</u>	Similar rate of subsequent stenosis between patients with/without cephalic arch stenosis (*)
Konner et al.	2000	Retrospective single-centre cohort study	Incident haemodialysis patients	72 months	Distal AVF Proximal AVF	<u>Patient survival</u> <u>Survival of the technique</u>	Lower survival rates in diabetic patients(*) Similar primary patency rates between groups (*)
Leapman et al.	1996	Retrospective single-centre cohort study	Incident haemodialysis patients	5 years	AVF	<u>Survival of the technique</u> DM vs. non-DM	1 year (*) 42% vs. 63% 5 year (*) 18% vs. 36%
Murphy et al.	2002	Retrospective single-centre cohort study	Incident haemodialysis patients	1 year	Proximal AVF	<u>Survival of the technique</u> DM vs. non-DM DM <65 vs. >65yo DM male vs. female	39% vs. 40% (p=N.S.) 59% vs. 59% (*) 69% vs. 47%
Ravani	2002	Prospective single-centre cohort study	Incident haemodialysis patients	3 years	Distal AVF Proximal AVF	<u>Survival of the technique</u> DM vs. non-DM DM	Primary patency HR=1.85, p=0.01 Cumulative patency HR=2.38, p=0.04 Similar results between distal and proximal AVF (*)

Saxena	2002	Prospective single-centre cohort study	Haemodialysis patients	4 years	AVF AVG Permanent CVC Subclavian CVC Femoral CVC	<u>Vascular access-related infection associated mortality</u> AVF (Ref.) 15% AVG 42% (p<0.0006) permanent CVC 33% (p<0.03) subclavian CVC 37.5% (p<0.001) femoral CVC 100% (p<0.0005) <u>Vascular access-related infections</u> AVF (Ref.) 0.04/patient-year AVG 1.07/patient.year permanent CVC 1.15/1000 catheter-days subclavian CVC 1.3/1000 catheter-days femoral CVC 1.5/1000 catheter-days	
Yeager	2002	Retrospective single-centre case-control study	Haemodialysis patients with finger gangrene	3 years	AVF	<u>Patient survival</u> (finger gangrene vs. no-finger gangrene) 52% vs. 49% (*)	
Konner	2002	Retrospective single-centre cohort study	Chronic kidney disease patients		Distal AVF Proximal perforating AVF Proximal non-perforating AVF	<u>Primary patency rate</u> Distal AVF 80% (*) Proximal perforating AVF >80% Proximal non-perforating AVF 50% <u>Cumulative patency rate:</u> Distal AVF 90% Proximal perforating AVF 80% Proximal non-perforating AVF 50% <u>Thrombosis rate:</u> Distal AVF 6.3 Proximal perforating AVF 0.8 Proximal non-perforating AVF 3.0	
AVF: arteriovenous fistula; AVG, arteriovenous graft; DM, Diabetes Mellitus * No effect measure reported							

Figure 1. Flow diagram of the study selection process



Supplementary Table I. Focused search strategy in CENTRAL and MEDLINE-
EMBASE databases

CENTRAL
<ul style="list-style-type: none"> • fistula*:ti,ab,kw • (shunt or shunts):ti,ab,kw • (graft or grafts*):ti,ab,kw • “blood vessel prosthesis”:kw • catheter*:ti,ab,kw • central next line*:ti,ab,kw • (AVF or AVG or CVC):ti,ab,kw • (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7) • dialysis:ti,ab,kw • (hemodialysis or haemodialysis):ti,ab,kw • (hemodiafiltration or haemodiafiltration):ti,ab,kw • (hemofiltration or haemofiltration):ti,ab,kw • “chronic kidney”:ti,ab,kw • “chronic renal”:ti,ab,kw • “kidney failure”:ti,ab,kw • (“end-stage kidney” or “end stage kidney” or “end-stage renal” or “end stage renal” or “endstage kidney” or “endstage renal”):ti,ab,kw • (CKF or CKD or CRF or CRD):ti,ab,kw • (ESKF or ESKD or ESRF or ESRD):ti,ab,kw • (“pre-dialysis” or predialysis):ti,ab,kw • (#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19) • MeSH descriptor Diabetes Mellitus, this term only • MeSH descriptor Diabetes Mellitus, Type 1 explode all trees • MeSH descriptor Diabetes Mellitus, Type 2 explode all trees • MeSH descriptor Diabetic Nephropathies explode all trees • diabet*:ti,ab,kw • (niddm or iddm):ab,ti,kw • (#21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27) • (#8 AND #20 AND #28)
MEDLINE
<ul style="list-style-type: none"> • randomized controlled trial.pt. • controlled clinical trial.pt. • randomi?ed.ab,ti. • placebo\$.ab,ti. • drug therapy.fs. • randomly.ab,ti. • trial\$.ab,ti. • group\$.ab,ti. • or/1-8 • Meta-analysis.pt. • exp Technology Assessment, Biomedical/ • exp Meta-analysis/ • exp Meta-analysis as topic/ • (health technology adj6 assessment\$).tw,ot. • hta.tw,ot. • (meta analy\$ or metaanaly\$ or meta?analy\$).tw,ot. • exp Cohort studies/ • Incidence.tw. • exp mortality/ • exp follow-up studies/

- mo.fs.
- prognos\$.tw.
- predict\$.tw.
- course.tw.
- exp survival analysis/
- (comment or editorial or historical-article).pt.
- Arteriovenous Fistula/
- Arteriovenous Shunt, Surgical/
- Blood Vessel Prosthesis/
- Blood Vessel Prosthesis Implantation/
- (vascular access or venous access).tw.
- (dialysis access or hemodialysis access or haemodialysis access).tw.
- Catheterization, Central Venous/
- fistula\$.tw.
- (graft or grafts).tw.
- (shunt or shunts).tw.
- prosthesis.tw.
- tunne\$.tw.
- catheter\$.tw.
- central line\$.tw.
- (AVF or AVG or CVC).tw.
- Kidney Failure/
- exp Renal Insufficiency, Chronic/
- (end-stage renal or end-stage kidney or endstage renal or endstage kidney).tw.
- (ESRF or ESKF or ESRD or ESKD).tw.
- (chronic kidney or chronic renal).tw.
- (CKF or CKD or CRF or CRD).tw.
- predialysis.tw.
- *Kidney Transplantation/ or exp *Peritoneal Dialysis/
- exp diabetes mellitus/
- Diabetes Mellitus, Type 1/
- Diabetes Mellitus, Type 2/
- Diabetic Nephropathies/
- diabet\$.tw.
- (niddm or iddm).tw.

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Date	03/09/2014

Manuscript title	Preferred haemodialysis vascular access for diabetic chronic kidney disease patients: a systematic literature review Luís Coentrão, Wim Van Biesen , Inout Nistor, Jan Tordoir, Maurizio Gallieni, Anna Marti Monros, Davide Bolignano
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