ANNEXES TO CHAPTER 4

Clinical Question XIV. What are the demographic, clinical and haemodynamic factors and variables with predictive power of thrombosis in an arteriovenous fistula that presents stenosis?

No studies were found that provided information for evaluating potential predictors of thrombosis risk specifically *in patients already diagnosed with stenosis* in the vascular access. Results are presented from studies that can answer the clinical question *indirectly*, and as it is not based on analysis of what happens in patients with vascular access stenosis, in general terms, the quality of evidence is low.

Several narrative reviews of the literature and original articles report that the main risk factor for thrombosis is the type of vascular access, with the risk for synthetic grafts and central venous catheters much higher than that for fistulae (Brattich 1999; Choudhury 2006; May 1997; Montagnana 2011). Montagnana (2011) states that the risk of thrombosis in vascular access sites using arteriovenous fistulae is 0.2 to 0.8 per patient-year, while it is 0.6 to 1.2 per patient-year in access sites with synthetic graft.	**Low quality**
A narrative review of recent literature (Montagnana 2011) considered thrombosis as a multifactorial disorder caused by a constellation of congenital and acquired factors, as well as environmental pro-thrombotic factors, which is also influenced by factors such as race, age and gender. They did not express definitive conclusions on which factors are associated with increased risk of vascular access thrombosis in patients on haemodialysis, but they did make a list of potential candidates, classifying them into two categories: – The first is <u>hereditary risk factors</u>: prothrombin 20210 polymorphism and different gene polymorphisms (transforming growth factor beta, the synthesis of nitric oxide, plasminogen activator-inhibitor 1, angiotensin-converting enzyme, and methylenetetrahydrofolate reductase). – The second is <u>acquired risk factors</u>, which include: diabetes, obesity, atrial fibrillation, hypertension, hyperhomocysteinaemia, hyperlipoproteinaemia, low levels of serum albumin, antiphospholipid antibodies, antibodies against the proteins D and S, erythropoietin, malnutrition and cytomegalovirus infection. Considering the <u>pathogenic mechanisms of thrombosis</u> in the vascular access, the factors are classified into three groups: - *factors that cause damage to endothelial cells*: hypertension, oxidative stress, "shear stress" (stress due to friction), inflammation, diabetes, uraemic toxins, lack of biocompatibility of artificial membranes, activated platelets, increase in circulating levels of TNF-alpha, fibromuscular intimal hyperplasia, cytomegalovirus infection. - *factors that cause blood stasis*: low inflow, low outflow, narrow lumen, hypovolaemia hypotension, hypoalbuminaemia. - *hypercoagulability*: platelet hyperactivity, decreased tissue plasminogen activator (t-PA), prothrombin 20210 polymorphism, antibodies against proteins D and S, anti-lipid antibodies, hyperhomocysteinaemia and hyperlipoproteinaemia.	**Low quality**

Haemodynamic factors	
The analysis of the ROC curve is ideal for helping with the decision about a diagnostic test when, as in this case, a cut-off point needs to be set in order to classify a person as at-risk of thrombosis or not. The ROC curve is a graphical representation of sensitivity or the rate of true positives against the false positive rate (1 - specificity). The narrative review of the literature by Work (2011) presents information about several observational studies analysing the utility of the blood flow study for predicting the risk of vascular access thrombosis: – The prospective study by McDougal (2001), which studied venous pressure, and surveillance of graft flow in predicting thrombosis of the graft in 71 patients with grafts for vascular access, in whom 41 cases of thrombosis occurred. The study found an increased risk of thrombosis of the graft in grafts with diminished access blood flow when a risk factor analysis was used, as occurred in the May study (1997). However, when analysed by means of curves, these authors found that the measurement of dialysis access blood flow was not a useful clinical test due to the high rate of false positives. They concluded that a static or dynamic venous pressure alone could not predict thrombosis of the graft. – The prospective study by Dember (2002), in which measurements of static venous pressure were carried out monthly for predicting thrombosis of the graft, in 164 patients with upper limb grafts, 54% of whom had a thrombotic event during the study. Using ROC curve analysis, they found that the static venous pressure measurement was a poor predictor of subsequent thrombosis. They argue that the different thresholds for referring patients for a potential preventive intervention must result in many patients being badly classified, i.e. many patients may have been subject to an unnecessary invasive intervention and others who could have benefited from the intervention may not have been correctly diagnosed. They conclude that, "Not all cases of venous anastomosis stenosis lead to thrombosis of the graft" and, in addition "There is not currently any method for discriminating between non-problematic stenosis and stenosis that may result in thrombosis". – The Paulson study (1999; 2000) that followed up 80 patients with 83 grafts for 12 months, concluded that, on the basis of analysis of the ROC curve, single or repeated measurements for monitoring graft blood flow cannot predict thrombosis of the graft. They consider that to predict thrombosis risk, it is probably necessary to use information about several factors, not one single potential risk factor. The Work review (2011) also included studies that had analysed risk factors but without using the ROC curve approach, and concluded that the flow measurements were valid for predicting risk of thrombosis: the May study (1997), which only found increased risk in cases of decreased blood flow in the access; or the Neyra study (1998), which was more specific, defining risk as decrease in flow rate of over 15%. Therefore, if we go with the conclusions of studies that analysed the ROC curves, the methods for monitoring access flow are poor in predicting thrombosis of the graft, and may lead to many patients undergoing unnecessary and costly procedures.	**Low quality**
The Kapun study (2008) included 41 patients on haemodialysis with arteriovenous fistula and adequate haemodialysis (eKt/V ≥1.2). Two patient groups were defined: group A with 17 at-risk patients with AVF (recirculation ≥10%); and group B with 24 control patients with the good AVF functioning (recirculation <10%). During the study, there were 0.025 cases of	**Low quality**

thrombosis per patient-year in group A and none in group B. They therefore concluded that a high recirculation (recirculation ≥10%) is a substantial risk factor for the development of stenosis which progresses to thrombosis.	
The Singh study (2006) analysed 43 patients with functional grafts and concluded that in these patients, neither static nor dynamic venous pressure provided suitable sensitivity or specificity to predict thrombosis in access by graft. They concluded that decreased blood flow in the access was the best predictor of thrombosis in the graft.	**Low quality**
The Tessitore study (2003) evaluated the precision of the Qa measurement (ultrasound dilution blood flow rate), Qa adjusted for mean arterial pressure, and decreased in Qa over time in the detection of stenosis and prediction of thrombosis in an unscreened population of 120 patients on haemodialysis with fistula (91 fistulae located in the wrist and 29 in the middle of the forearm). All patients were analysed by fistulogram, which identified stenosis greater than 50% in 54 cases. They do not however provide separate analyses for the patients with stenosis. They conclude that the Qa measurement is the best predictor of early thrombosis (AUC, 0.981 +/- 0.013) with an optimal cut-off at less than 300 ml/min (efficiency, 94%).	**Low quality**
The Weitzel study (2003) specifically analysed the effect of the amount of time elapsed since a Doppler measurement of access flow for predicting thrombosis, by means of a retrospective review of 36 patients with vascular access implants. They studied the ROC curves and the sensitivity and specificity for various follow-up time intervals. The ROC curve analysis showed an increase in the test's discrimination for the shorter time intervals. The sensitivity and specificity for a commonly used monitoring threshold (600 ml/min) showed a specificity that changed little for follow-up intervals of 15 days to 6 months (88-93%). However, the sensitivity was low (21%) at 6 months, increased to 50% at 2 months, 67% at 1 month, and 100% at 15 days (a single event). They considered that the detection of a low blood flow by Doppler ultrasound predicted thrombosis in the short-term. These data also mean that the discriminatory value of monitoring the access flow appears to be highly dependent on the timing of the measurement, improving with shorter measurement time intervals.	**Low quality**
The Wang study (1998) intended to evaluate whether repeated measurement of access blood flow (Qac) using the ultrasound dilution technique would be able to predict access failure in patients on haemodialysis. 131 patients were evaluated at 8 week intervals for 6 months. They studied the incidence of thrombosis within each 8-week time period. During the 6-month follow-up, 36 thrombotic events occurred in 27 of 68 polytetrafluoroethylene (ePTFE) grafts, and only six thrombotic events in 5 of 63 arteriovenous fistulae. The relative risk for access thrombosis for patients with ePTFE grafts was 5.6 times greater than for patients with AV fistulae. Qac was significantly lower in thrombotic compared with patent ePTFE grafts (958 +/- 506 ml/min vs 1141 +/- 482 ml/min, $p<0.05$). A significant relationship was found between the incidence of subsequent ePTFE graft thrombotic events and Qac ($p<0.001$). Compared with accesses with high blood flow (1100-1400 ml/min), the risk for subsequent thrombosis tripled in grafts with a Qac of less than 500 ml/min. This relationship was not observed in patients with AVF.	**Low quality**

Hyperhomocysteinaemia	
Four published studies were found that analyse whether high levels of homocysteinaemia are a risk factor for vascular access thrombosis in patients on haemodialysis. However, none of these studies were conducted only in patients with vascular access stenosis: Tamura (1998), Bowden (2002), Lévesque (2003) and Saifan (2013). None of the four studies showed an increased risk of thrombosis in patients with higher levels of homocysteinaemia.	**Low quality**
Summary of evidence	
There were no studies that analysed different possible thrombosis risk factors, either separately or otherwise, specifically in patients with access stenosis.	
The results of studies that analysed the utility of different measurements of blood flow for predicting access thrombosis and used analysis of ROC curves suggest that the methods for monitoring access flow are poor in predicting thrombosis of the graft, and may lead to many patients undergoing unnecessary and costly procedures.	**Low quality**
No single factor on its own has been found to be a good predictor of vascular access thrombosis risk.	**Low quality**
None of the published studies found increased risk of thrombosis in patients with higher levels of homocysteinaemia.	**Low quality**
Patients' values and preferences *No relevant studies related to this aspect have been identified.*	
Use of resources and costs *No relevant studies related to this aspect have been identified.*	
Recommendations [Proposal]	
Weak	We suggest that the results of blood flow analysis or hyperhomocysteinaemia should not be used in isolation to predict thrombosis risk in patients with vascular access stenosis.
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Table 1. REVIEWS AND STUDIES EXCLUDED

Study	Cause for exclusion
Brattich 1999	Narrative review. More up-to-date reviews are available, from 2011.
Choudhury 2006	Narrative review. More up-to-date reviews are available, from 2011.
Krivitsky 2001	Narrative review. More up-to-date reviews are available, from 2011.
Smits 2000	Narrative review. More up-to-date reviews are available, from 2011.
Reinhold 2011	Narrative review. In German.
Planken 2008	Study on angiography in patients before deciding on vascular access.
Wang 2000	Study that does not analyse the risk of thrombosis separately.
Sands 2000	Analysed perioperative exposure to topical bovine thrombin
Vannorsdall 2003	Analysed perioperative exposure to topical bovine thrombin