ANNEXES TO CHAPTER 4

Clinical Question XI. Can regulated Doppler ultrasound performed by an experienced examiner replace angiography as the gold standard to confirm significant arteriovenous fistula stenosis?

The principal cause of vascular access failure is the progressive stenosis of the lumen as a result of hyperplasia of the intima which restricts the blood flow and can lead to thrombosis. Detecting the stenosis before thrombosis occurs and performing therapeutic angioplasty increases the duration of the vascular access. This in turn reduces the number of times vascular access for haemodialysis has to be created in the patient's lifetime and decreases the morbidity associated with access failure.

Digital subtraction angiography is the standard technique for diagnosing vascular access fistula or graft dysfunction in patients on haemodialysis. As this is an invasive procedure and also involves exposure to ionising radiation, there is interest in the possibility of using non-invasive or minimally invasive methods when vascular access stenosis is suspected. Doppler ultrasound is portable and costs less in terms of equipment and consumables, making it an attractive technique for patients, healthcare professionals and dialysis units.

Duplex-Doppler ultrasound (DDU) does have a number of disadvantages (operator dependent, interference of dressings, wounds and calcification in the vessels impeding assessment of anastomosis stenosis). However, the advantages associated with the technique (non-invasive, no ionising radiation or iodine contrast, cheap and accessible) mean that it is increasingly being used before angiography to study peripheral vascular accesses, as the information the Doppler provides is not only on the fistula (morphological) but also on the efferent artery and the flow rate (*inflow and outflow*) (Moreno 2013).

In relation to which criteria to use to classify stenosis as significant for Doppler ultrasound, generally the authors agree on three criteria. The first is reduction of 50% or more in the diameter of the efferent vein (Robbin 1998; Doelman 2005; Moreno 2013). The second is haemodynamic: a peak systolic velocity double or more than double compared to the other side of the graft (Robbin 1998), or increase of more than 100% in the flow rate compared to the adjacent normal segment (Moghazy 2009; Moreno 2013). Labropoulos (2007) considered that a peak vein velocity ratio >2.5 across the stenosis is the best criterion for detecting a pressure gradient of 3 mmHg. The third criterion is the detection of a focal overlapping region (*aliasing*) in colour Doppler study (Moghazy 2009; Moreno 2013).

We were unable to find any randomised clinical trials or other controlled studies that analyse the clinical consequences of testing patients with suspected stenosis-related dysfunction of haemodialysis vascular access (due to palpation, auscultation or abnormal flow rate during haemodialysis, or difficulty introducing cannula into the access) using Doppler ultrasound only compared to the usual practice of ultrasound followed by angiography when the ultrasound concludes that there is stenosis. As the results for this clinical question are derived from indirect evidence on the diagnostic performance of these procedures, the quality of evidence available is low.

We were able to find seven studies that provide data on the diagnostic efficacy of Doppler ultrasound compared to angiography for the diagnosis of significant stenosis of the vascular access in patients with clinically suspected stenosis. In three of the studies, all patients had a fistula for haemodialysis (Cansu 2013; Moghazy 2009; Salman 2010). One study only had patients with grafts (Robbin 1998), and the other three included patients with fistulae and patients with grafts (Doelman 2005; Middleton 1988; Moreno 2013).	
Studies with fistula patients only	
The study by Cansu (2013) analyses the combined use of Doppler ultrasound and CT angiography (multidetector computed tomography (MDCT) angiography) in the analysis of 35 stenotic lesions in 41 patients with dysfunctional haemodialysis fistulae. When digital subtraction angiography or surgery were taken as the gold standard, colour Doppler ultrasound detected 26 of the 35 stenosis lesions and gave three false positives that were not confirmed in angiography or surgery, resulting in a sensitivity of 74.2%, a specificity of 90.6%, PPV 89.6%, NPV 76.3% and a precision of 82.6%. In MDCT angiography, the results were consistent with those of surgery or angiography in 34 out of the 35 stenosis lesions. There was one false negative and two false positives, resulting in a sensitivity of 97.1%, a specificity of 93.7%, VPP 94.4%, NPV 96.7% and a precision of 95.4%. With the combined use of the two techniques, all values were 100%. In the publication they provide disaggregated data on the precision of the techniques for different stenosis sites (juxta-anastomotic, drainage vein, central venous, or artery that feeds the stenosis).	**Low quality**
The study by Moghazy (2009) analysed the reliability of Doppler ultrasound in 55 patients with fistula and dysfunctions in the vascular access. Ultrasound detected 23 cases of stenosis which were confirmed by arteriogram. However, in two patients it was undetermined, in both cases due to incomplete visualisation of the subclavian vein, but found to be positive for stenosis in the arteriogram. This meant sensitivity of 92%.	**Low quality**
The study by Salman (2010) assessed the reliability of Doppler ultrasound versus arteriogram in 103 patients who had been referred for intervention on the fistula due to vascular access problems. Ultrasound diagnosed 51 cases of stenosis, 50 of which were confirmed by angiogram and one not. Angiography detected five cases of stenosis which had not been detected by ultrasound examination. Ultrasound, compared to angiography, showed a sensitivity of 91%, a specificity of 98%, a positive predictive value of 98% and a negative predictive value of 90%.	**Low quality**
Studies with synthetic graft patients only	
The study by Robbin (1998) analysed 34 patients with clinically suspected stenosis, in whom angiogram detected 40 cases of stenosis of at least 50% of the diameter. Only 37 were detected by ultrasound, with the criterion being that the ratio of the peak flow rate before and after was	**Low quality**

2 or higher. This meant sensitivity of 92% for the ultrasound.	
Studies with fistula or synthetic graft patients	
The study by Doelman (2005) included 111 patients with significant stenosis (>50%) in 433 vascular segments diagnosed by angiogram. The sensitivity and specificity of Doppler ultrasound for the detection of vessel segments with significant stenosis were 91% (95% CI, 84-95%) and 97% (95% CI, 94-98%) respectively. A positive predictive value of 91% (95% CI, 84-95%) and a negative predictive value of 97% (95% CI, 94-98%) were found.	**Low quality**
Middleton (1989) studied 28 patients, 9 with fistula and 19 with graft synthetic, all suspected to have various access complications which were analysed by both angiography and colour Doppler ultrasound. Colour Doppler ultrasound correctly detected 20 of the 23 instances of stenosis diagnosed by angiography, meaning a sensitivity of 87% (95% CI: 0.66-0.97).	**Low quality**
Moreno (2013) analysed 159 patients with dysfunctional peripheral vascular accesses (118 stenosis, 19 thrombosis and 14 no abnormalities). Duplex-Doppler ultrasound was compared with angiography and clinical and analytical follow-up for 3 months (if the angiogram was negative). A total of 115 of the 118 cases of stenosis were detected on ultrasound. Duplex Doppler ultrasound showed a sensitivity of 0.98 (95% CI: 0.88-1), a specificity of 0.74 (95% CI: 0.66-0.81), a positive predictive value of 0.96 and negative predictive value of 0.82, with a positive likelihood ratio of 3.70 and negative likelihood ratio of 0.03.	**Low quality**
Doppler ultrasound as gold standard test in the diagnosis of significant stenosis of access	
A combined analysis in a meta-analysis (MetaAnalyst program) with the available data from the four studies from the last 10 years which also provide complete data allowing estimation of the sensitivity and specificity of Doppler ultrasound versus angiography for the diagnosis of significant stenosis in patients with clinically suspected vascular stenosis (Cansu 2013; Doelman 2005; Moreno 2013; Salman 2010) included data from 755 patients, 319 of whom were diagnosed with significant stenosis by angiogram, representing a prevalence of 42.3%. The meta-analysis showed overall values of sensitivity of 89.3% (95% CI: 84.7-92.6%) and a specificity of 94.7% (95% CI: 91.8-96.6%) for Doppler ultrasound (Tables 2 and 3). These values are high, but they are insufficient to be able to consider ultrasonography as a candidate to replace ultrasound angiography as diagnostic gold standard for confirming significant stenosis of vascular access. No test that leaves 10% of cases undetected can be considered as a diagnostic gold standard for confirmation of a disease.	**Low quality**

Summary of evidence	
Standard Doppler ultrasound performed by an experienced examiner cannot replace angiography as diagnostic gold standard for the confirmation of significant VA stenosis because of its levels of sensitivity (89.3%) and specificity (94.7%).	**Low quality**
There are no controlled studies that assess the clinical consequences of testing patients with suspected significant stenosis-related dysfunction of haemodialysis vascular access using Doppler ultrasound only or angiogram.	

Patients' values and preferences

No relevant studies related to this aspect have been identified. It seems logical to assume that if clinical outcomes were the same, patients would prefer non-invasive techniques that do not involve exposure to radiation. However, the greater reliability of angiography means that angioplasty is performed only in those who really do have significant stenosis.

Use of resources and costs

No relevant studies related to this aspect have been identified. Ultrasound is a less expensive technique than angiography. A diagnostic approach of starting with ultrasound and reserving angiography for repeatedly suspected cases that show negative on ultrasound would probably be more cost effective than performing angiograms on all patients with suspected stenosis.

Recommendations [Proposal]	
Weak	We do not recommend using Doppler ultrasound to replace angiography as gold standard for the confirming diagnosis of significant VA stenosis.

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Table 1. STUDIES EXCLUDED

Study	Cause for exclusion
Arbab-Zadeh (2002)	Analyse intravascular ultrasound not external ultrasound
Davidson (1991)	Analyse intravascular ultrasound not external ultrasound
Dousset (1991)	22 patients, of whom only four had suspected impairment due to increased venous pressure in haemodialysis (>180mmHg); for the other 18 patients there is no mention of any signs of suspected impairment in vascular access.
Kudlicka (2012)	They analysed the residual diameter in 20 cases of significant stenosis by ultrasound and angiography, which they used as additional criteria for diagnosis of stenosis at their site, and the results were similar with both methods: 1.69 ± 0.05mm for ultrasound and 1.65 ± 0.59 for angiography. They also analysed the repeatability of the ultrasound residual diameter measurements and their reproducibility versus angiography, by calculating the coefficients of variation (CV). The coefficient of variation was 3.17 ± 2.76% for repeatability and 18.0 ± 15.6% for reproducibility. They conclude that a residual diameter of 2.0 mm should be included as an additional criterion for significant stenosis, and that this can also be used for monitoring arteriovenous grafts.
Labropoulos (2007)	Study on central vein stenosis conducted in patients with a variety of medical conditions such as liver transplant, cancer and haemodialysis, but only seven of the patients were on haemodialysis and there is no breakdown of the analysis for these patients.
Nonnast-Daniel (1992)	Not on patients with clinically suspected stenosis. These were patients who underwent surgical intervention for impaired access, were diagnosed with stenosis from macroscopic inspection during surgery, and then had Doppler ultrasound to check the diagnostic reliability of the technique.
Roca-Tey (2005)	Does not provide information to allow sensitivity or specificity of colour Doppler ultrasound to be calculated versus angiography. The objectives were: 1) to analyse certain morphological and functional parameters of the VA by colour Doppler ultrasound; and 2) to carry out a study comparing Doppler ultrasound and the Delta-h method in the determination of blood flow in the VA.
Schwarz (2003)	Study with 59 patients on haemodialysis via arteriovenous fistula, but there is no indication of clinically suspected impaired access. They compared Doppler ultrasound and ultrasound dilution with fistulography. 41 patients were diagnosed with access stenosis, and the *area under the curve* for the colour Doppler ultrasound was 0.80 (95% CI: 0.65 to 0.94). They thought the optimal cut-off value for prediction of stenosis by colour Doppler ultrasound was of 390 ml/minute, with sensitivity of 76%, specificity of 78% and a positive predictive value of 89%.
Tordoir (1989)	Study on 58 patients of whom 47 had no clinical suspicion of stenosis.

Table 2. Recent studies providing data to calculate sensitivity and specificity of ultrasound

	True Positive	False Positive	False Negative	True Negative	Sensitivity [95% CI]	Specificity [95% CI]
Cansu 2013	26	3	9	26	0.74 [0.57, 0.88]	0.90 [0.73, 0.98]
Doelman 2005	101	10	10	311	0.91 [0.84, 0.96]	0.97 [0.94, 0.98]
Moreno 2013	115	5	3	33	0.97 [0.93, 0.99]	0.87 [0.72, 0.96]
Salman 2010	50	1	5	47	0.91 [0.80, 0.97]	0.98 [0.89, 1.00]

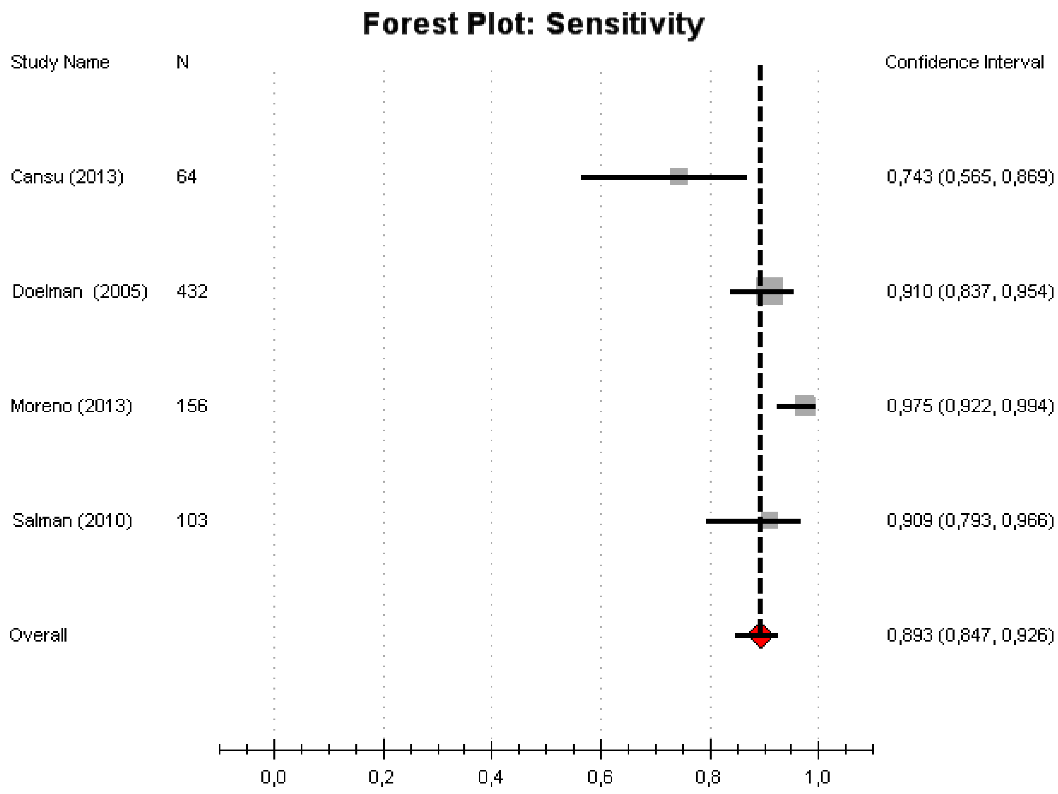
The four studies included 755 patients among them with 319 cases of significant stenosis, representing a prevalence of 42.3%.

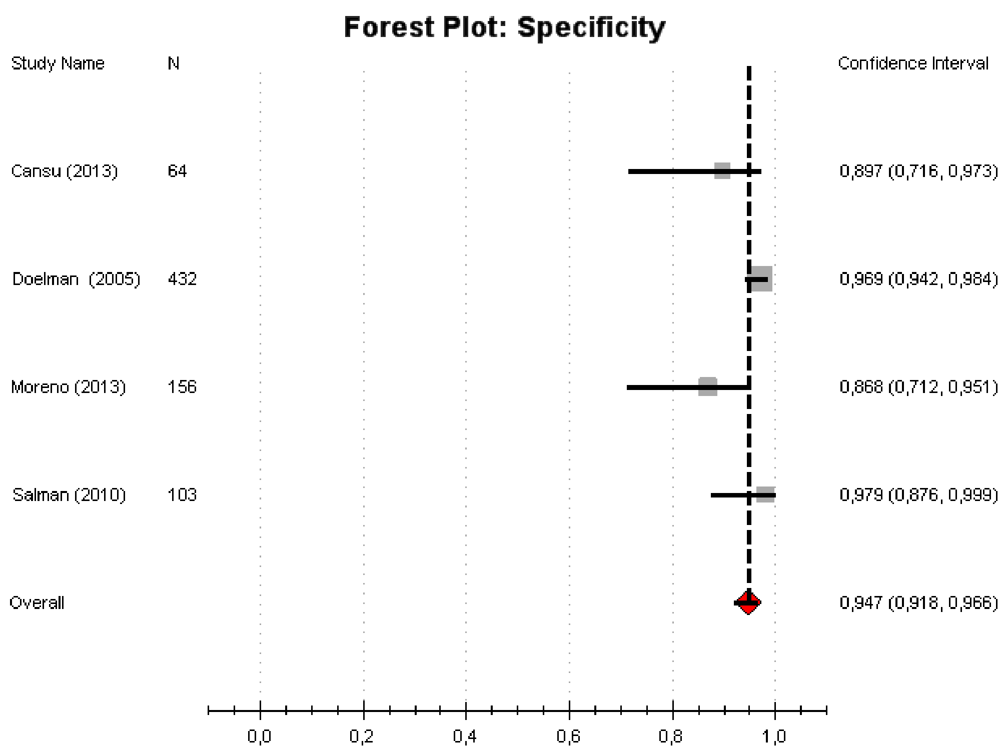
Table 3. Meta-analysis of data from four studies using MetaAnalyst

		Confidence interval: 95%	
	Estimated	Low	High
Sensitivity	0.893	0.847	0.926
Specificity	0.947	0.918	0.966
+ve predictive value	0.931	0.894	0.956
-ve predictive value	0.918	0.882	0.944
Precision	0.932	0.910	0.949
DOR	183.914	96.254	351.408
LR+	16.123	10.428	24.926
LR-	0.126	0.089	0.179

Sensitivity: 89.3% (95% CI: 84.7-92.6%)
Specificity: 94.7% (95% CI: 91.8-96.6%)

The graphs below show the calculations plus their 95% confidence intervals for sensitivity and specificity of the Doppler ultrasound, both for each individual study and for pooled data; the calculations were made with MetaAnalyst (free access program) on 11 November 2013.


Forest Plot: Sensitivity
Study Name
N
Confidence Interval
Cansu (2013)
64
0,743 (0,565, 0,869)
Doelman (2005)
432
0,910 (0,837, 0,954)
Moreno (2013)
156
0,975 (0,922, 0,994)
Salman (2010)
103
0,909 (0,793, 0,966)
Overall
0,893 (0,847, 0,926)
0,0
0,2
0,4
0,6
0,8
1,0


Forest Plot: Specificity
Study Name
N
Confidence Interval
Cansu (2013)
64
0,897 (0,716, 0,973)
Doelman (2005)
432
0,969 (0,942, 0,984)
Moreno (2013)
156
0,868 (0,712, 0,951)
Salman (2010)
103
0,979 (0,876, 0,999)
Overall
0,947 (0,918, 0,966)
0,0
0,2
0,4
0,6
0,8
1,0