Peripheral arterial disease: clinical and cost comparisons between duplex US and contrast-enhanced MR angiography - a multicenter randomized trial


Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The study examined two diagnostic strategies for patients with peripheral arterial disease (PAD). The strategies were duplex ultrasonography (US) and contrast-enhanced magnetic resonance angiography (MRA). Given the variety of models of imaging equipment, each participating centre was allowed to use the imaging protocols for both duplex US and MRA that were considered optimal.

Type of intervention
Diagnosis.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients with intermittent claudication or critical ischaemia, who had an ankle-brachial pressure index (ABPI) of less than 0.90. Patients were excluded if they had contraindications to MRA, or had already undergone imaging workup that suggested that revascularisation was needed.

Setting
The setting was an outpatient clinic. The economic study was carried out in the Netherlands.

Dates to which data relate
The clinical and economic data were gathered between January 2002 and September 2003. The price year was 2002.

Link between effectiveness and cost data
The costing was carried out prospectively on the same sample of patients as that used in the analysis of effectiveness.

Study sample
Power calculations were performed in the preliminary phase of the study to determine the sample size necessary to detect a statistically significant difference between groups in terms of quality of life (QoL). A sample of 357 patients was required to detect a difference of 15% with a power of 80% at a significance level of 5%.

All patients with PAD who were referred by the vascular surgeon for imaging workup, to determine the feasibility and choice of revascularisation procedure at the study centres, were initially assessed for eligibility. Patients who needed to undergo imaging workup within 3 days were excluded. Of the 720 patients initially assessed, 363 were excluded (mainly because they did not meet the inclusion criteria or because they were emergency cases; only 14 refused to participate). Thus, 357 patients were included in the study sample, of which 180 were allocated to the MRA group and 177 to the
duplex US group. However, 2 patients in the MRA group and 3 patients in the duplex US group did not receive any test (owing to death or early withdrawal from the study). Consequently, the final sample consisted of 178 patients (66% men) in the MRA group and 174 patients (70% men) in the duplex US group. The mean age of the patients was 65 (+/- 11) years in both groups. The reasons for patient exclusion or refusal were reported.

**Study design**
This was a prospective, randomised study that was carried out at two university hospitals and one general hospital in the Netherlands. Experienced ultrasonographers performed all the procedures. Randomisation was performed by telephone using a computer-generated block design, with a block size of eight. The length of follow-up was 6 months. No patient was lost to follow-up, except for those who died or withdrew before receiving the imaging study. Blinding was not feasible given the nature of the procedure.

**Analysis of effectiveness**
The primary clinical end points were therapeutic confidence, changes in severity of disease and changes in QoL. Therapeutic confidence was assessed with respect to the confidence of the radiologists and vascular surgeons in their ability to make a therapeutic decision on the basis of the results from each diagnostic modality. This end point was rated on a scale from 0 (no confidence) to 10 (extremely confident). Changes in disease severity were evaluated using four measures: the Rutherford classification, the treadmill walking distance, ABPI at rest and ABPI after exercise. Changes in QoL were assessed using the Rating Scale questionnaire, two generic questionnaires (Short-Form 36 and EuroQol 5D) and a disease-specific questionnaire (the VasenQol). QoL questionnaires were filled at baseline, 2 weeks, 3 months and 6 months, and the return rate was very high (98%, 95%, 91% and 88%, respectively). The number of further imaging tests needed after initial duplex US or MRA was also reported.

The analysis of the clinical study was conducted on an intention to treat basis. At baseline, the study groups were comparable in terms of the clinical and demographic characteristics. However, co-morbidities were observed slightly more frequently in the MRA group.

**Effectiveness results**
The mean therapeutic confidence score was 8.2 in the MRA group and 7.5 in the duplex US group. The difference was statistically significant. (p<0.001).

None of the differences in the other clinical end points (changes in disease severity and QoL) reached statistical significance.

The number of additional vascular imaging examinations was reduced by 42% in the MRA group, (p<0.001).

The total number of additional diagnostic digital subtraction angiography examinations was reduced by 63% in the MRA group compared with the duplex US group, (p=0.001).

**Clinical conclusions**
The effectiveness analysis showed that the use of MRA improved therapeutic confidence in comparison with duplex US without affecting QoL or disease severity. A significant reduction in the number of additional diagnostic examinations was also observed.

**Measure of benefits used in the economic analysis**
The health outcomes were left disaggregated and no summary benefit measure was used in the economic evaluation. In effect, a cost-consequences analysis was performed.

**Direct costs**
The viewpoint of the cost analysis was that of the hospital. Thus, the categories of costs included in the analysis were those associated with diagnostic tests, outpatient visits, physician services and therapeutic services. A breakdown of cost items was provided for each category and the authors described the components of each cost category. The method used to estimate the equipment cost for each diagnostic procedure was also described. The unit costs and the quantities of resources used were presented separately for all items. The costs were estimated using a standardised approach in the Dutch setting. Most of the costs were based on national estimates, whereas a few items were costed using a comparable study. Data on resource use were collected at baseline and 6 months after patient enrolment in each of the three hospitals involved in the study. Discounting was not relevant as the costs were incurred during 6 months. The price year was 2002.

Statistical analysis of costs
Cost-differences between the groups were tested using Student's t-test. As in the analysis of clinical end points, economic data were analysed using the intention to treat principle, thus all patients initially included in the study sample were taken into account in the economic analysis. The power analysis that was performed for the clinical outcomes was valid also for the detection of statistically significant differences in total diagnostic costs and total costs. A logistic regression analysis was also performed to take the potential impact of confounding factors into consideration.

Indirect Costs
Productivity costs were not considered.

Currency
Euros (EUR) and US dollars ($). The exchange rate in January 2002 was EUR 0.90 = $1.

Sensitivity analysis
A one-way sensitivity analysis was carried out to assess the impact of a reduction in the investment cost of MRA on diagnostic costs. The cost reduction was arbitrarily set at 50% of the baseline price. A sub-group analysis was also performed to take into account the three different hospitals participating in the study.

Estimated benefits used in the economic analysis
See the 'Effectiveness Results' section.

Cost results
The total diagnostic costs per patient were EUR 532 (95% confidence interval CI: 308 to 960) in the MRA group and EUR 356 (95% CI: 57 to 1,434) in the duplex US group. The difference of EUR 167 (95% CI: 79 to 255) was statistically significant, (p<0.001).

Specifically, MRA was associated with statistically significantly higher initial test costs (EUR 473 versus EUR 105; p<0.001) that were not offset by a reduction in diagnostic test costs during the follow-up.

When outpatient visits, percutaneous interventions and surgical procedures during the follow-up were also considered, the total costs per patient were EUR 3,012 (95% CI: 499 to 10,474) in the MRA group and EUR 2,713 (95% CI: 180 to 7,769) in the duplex US group. The difference of EUR 272 (95% CI: -377 to 921) was not statistically significant, (p=0.41).

The sensitivity analysis also showed that with a 50% cost reduction in the investment cost of MRA, the total diagnostic costs per patient were comparable between groups. The sub-group analysis revealed that differences in costs were not statistically significant when the three hospitals were analysed separately.
Synthesis of costs and benefits
A synthesis of the costs and benefits was not relevant as a cost-consequences analysis was carried out.

Authors' conclusions
Contrast-enhanced magnetic resonance angiography (MRA) led to a higher therapeutic confidence and a lower need for further diagnostic imaging studies in comparison with duplex ultrasonography (US) in patients with peripheral arterial disease (PAD). Although diagnostic costs were higher with MRA, the total costs to the hospital were comparable.

CRD COMMENTARY - Selection of comparators
The authors justified the choice of the two health technologies. Duplex US represented the conventional diagnostic approach for PAD, while contrast-enhanced MRA was not commonly used as the initial imaging approach, although many studies had shown its higher accuracy. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The analysis of effectiveness was based on an RCT, which was appropriate for the study question. RCTs are usually associated with a high internal validity given the randomised nature of their design. The size of the sample of patients was justified on the grounds of statistical calculations, which should have ensured the enrolment of an appropriate number of participants. Details about the sample selection process and the randomisation procedure were given. The reasons for the exclusion of some patients were explicitly reported. Moreover, the use of the intention to treat principle will have enhanced the robustness of the analysis. Several clinical measures and QoL scores were used. The return rate of the questionnaires was very high. The authors stated that blinding was not possible given the nature of the diagnostic intervention, which was apparent to both patients and health care professionals. The multi-centred nature of the study enhances the representativeness of the study sample. Overall, the analysis of the clinical outcomes appears to have been performed satisfactorily.

Validity of estimate of measure of benefit
No summary benefit measure was used since a cost-consequence analysis was performed.

Validity of estimate of costs
The analysis of the costs was consistent with the authors' stated perspective. It appears that all the relevant categories of costs have been included. The authors stated that the use of a broad perspective (i.e. societal) is often recommended. However, as most patients enrolled in the study were retired, the choice of a hospital perspective might have been more appropriate. A breakdown of the cost items was presented and extensive information on resource consumption and unit costs was given. This aspect of the analysis will help its replication of the analysis in other settings. The sources of costs were presented for all items and represent typical Dutch sources. Statistical analyses of the costs were performed, not only to test the significance of cost-differences but also to take the potential impact of confounding factors into account. The price year was reported, which will assist reflation exercises in other time periods. A further strength of the analysis was the fact that the economic analysis had sufficient power to detect statistically significant differences between groups.

Other issues
The authors did not compare their findings with those from other studies. They also did not address the issue of the generalisability of the study results to other settings. Therefore, the external validity of the analysis was low. The authors stated that it would have been interesting to have performed a sub-group analysis of patients with critical ischaemia, who would be likely to benefit the most from the diagnostic strategy. However, the size of this group of patients was too small to permit a robust analysis. In general, the main strength of the study appears to have been the detailed description and statistical analysis of all cost components.

Implications of the study
The study results suggest that the two diagnostic approaches for patients with PAD are similarly effective and costly, although a higher therapeutic confidence is associated with MRA. However, since both strategies have advantages and disadvantages, the authors stated that the choice of the diagnostic option should be based on the local expertise and cost consideration relevant to the specific health care institution.
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