Is diagnosis and treatment of renovascular stenosis cost efficient?

Sir,

The recent invited opinion on ‘Diagnosis and treatment of renovascular stenosis (RVS)—a cost-benefit analysis’ [1] raises some topical and important issues. Few would argue that an increased awareness of costs is necessary in all those practising medicine in the 1990s. However, many clinicians have an inherent uneasiness about combining economics and health care.

In recent years systematic literature reviews have helped highlight strengths and weaknesses in clinical research. The increasing demands on clinical trials’ methodology must be matched by similar demands on published economic evaluations. Both contribute to the evidence base for policy makers and guideline committees. Therefore when health economics is used, particularly by non-economists, the methods must be sound. It has recently been shown that this may not always be the case [2].

The evidence for economic evaluations should be sought systematically and weighted according to quality. Methods must be made explicit, and assumptions should always be accompanied by ‘sensitivity analyses’ to demonstrate how a variation in that assumption might have affected the results.

From the information given by Radermacher and Brunhorst evidence was not systematically sought or weighted according to quality. Assumptions are acknowledged, but no attempt has been made to apply sensitivity analysis to them. For example, a figure of 2.6% is calculated as the percentage of patients with RVS who progress to ESRD. To calculate this requires knowledge of the number of patients with RVS in Germany and the proportion of incident ESRD patients with RVS. However, the authors use the proportion of prevalent ESRD patients with RVS when calculating the value 2.6%. This is clearly inappropriate. Patients with vascular disease have a much lower survival than those without. They therefore form a higher proportion of the incident compared to the prevalent population of patients with ESRD. Also, the denominator is based on the approximation that 20% of the German general population (80 million) have hypertension and 1% of such patients will have RVS. An absolute variation of 0.5% in the latter assumption could mean variation from 80,000 to 240,000 people—a three-fold difference. This has obvious implications for intervention costs, numbers progressing to ESRD and therefore overall conclusions.

Quantifying the uncertainty of such assumptions, and the impact that fluctuations in these assumptions have on results, is essential to inform decision-making. If we, as non-economists, chose to include economic evaluations in our work we must use the validated methods that already exist.

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Reply

Sir,

Dr Caskey correctly states, that the incidence rate of patients with renovascular disease requiring renal replacement therapy rather than the prevalence rate should be used to calculate the percentage of patients suffering from renal artery stenosis who will eventually proceed to end-stage renal disease. We actually used incidence data which were extracted from an US publication (Mailloux (1994) AJKD; 24 pp. 622) which is cited in the paper and reports an incidence rate of 10–15%. Unfortunately, incidence data are not available for the German population, as we have once more confirmed with ‘Quasi-Niere’, the German registry for patients with end-stage renal disease.

We agree with Dr Caskey that one should try to quantify the uncertainty of one’s assumptions. However, if the reported data show too great a variation, no conclusion regarding cost benefits could be drawn from them. We therefore think that an educated guess as to the ‘true’ numbers better serves the purpose of our review. We calculated the prevalence of patients with RAS in Germany assuming that 20% of the overall population suffer from hypertension and 1% of this number suffered from renal artery stenosis. There are five large studies reporting on the prevalence of RAS in a hypertensive population. The possible variation is actually larger than the one suggested by Dr Caskey, prevalence rates of renal artery stenosis in the hypertensive population ranging from 0.2 to 4% have been reported. Using this wide range of prevalence rates of renal artery stenosis in unselected hypertensive populations and assuming an incidence of renal artery stenosis in patients with end-stage renal disease ranging from 10 to 15%, a range of 0.6–19.4% of patients with RAS proceeding to end-stage renal disease could be calculated. This would amount to possible cost savings (reduced need for renal replacement therapy) in this patient group ranging from DM 2400 to DM 77600. Pick your choice.

Recalculating our data of cost differences between the different apparative screening tests, using the extreme ranges of these prevalence data, would alter the total cost to detect renal artery stenosis and perform angioplasty on a single patient as follows (data reported as ranges): Renovasography: DM 19818–34068; Spiral CT DM 13959–30209; NMR-Angiography DM 21792–36042; Colour duplex sonography DM 13773–28023; Capitoprí-enhanced scintigraphy DM 14719–28969. Prevalence rate after clinical screening however, has the greatest influence on total cost. Recalculating our data for a prevalence rate of renal artery stenosis after clinical screening ranging from 1% (i.e. no screening was performed) to 20%, the cost of colour duplex sonographic screening to detect and treat a single patient with renal artery stenosis would range from DM 28023 to 69356 and for a more costly apparative screening method.

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Letters

Increased plasma GDNF levels in patients with chronic renal diseases

Sir,

Glial cell-line-derived neurotrophic factor (GDNF) is a member of the transforming growth factor (TGF) superfamily and is considered to be a physiological trophic factor for neurons [1]. During fetal development, GDNF is highly expressed in metanephric kidneys, as well as in the nervous system [2,3], and GDNF-deficient mice completely lack kidneys [4-6]. GDNF signaling is mediated through the c-ret proto-oncogene [7]. During kidney morphogenesis, c-ret and GDNF are expressed by abutting cellular population [9]. Ret mRNA is localized in the epithelial cells of the branching ureteric bud, whereas GDNF is produced by the surrounding metanephric mesenchymal cells [7]. Moreover, GDNF has been shown to be a growth factor for mesangial cells and thus has been implicated to be a player in the genesis of progressive renal damage [8]. However, little is known about GDNF's behavior in the presence of renal dysfunction. We report here that chronic renal failure patients have very high plasma GDNF level.

Patients and methods. The plasma GDNF levels of 15 normal individuals who had normal routine biochemical values, and of 45 chronic renal failure (CRF) patients on regular hemodialysis (from 3 months to 15 years) were evaluated (mean age ± standard error of the mean (SEM), 60.2 ± 1.97 years). Of the CRF patients, 18 suffered from diabetic nephropathy (mean ± SEM, 65.8 ± 4.24 years), 11 from nephrosclerosis (mean ± SEM, 66.5 ± 4.52 years), and 16 from chronic glomerulonephritis (mean ± SEM, 56.3 ± 2.63 years). No acute disorders were present during the 1 month prior to the study. Blood samples of CRF patients were taken immediately before hemodialysis. Blood samples of normal subjects were taken at 9 am. The plasma was kept frozen at −80°C until assayed. GDNF was measured with a sandwich ELISA kit (Promega, USA) that detects human GDNF but not TGF-beta or nerve growth factor (NGF). The detection limit of GDNF assay was 2 pg/ml. TGF-beta-1 levels were quantified using ELISA (R&D systems, USA). Overall differences between the groups were analyzed with the Mann–Whitney’s U test. Correlation coefficients between variables were calculated by Spearman’s non-parametric correlation analysis.

Results. Table 1 summarizes the plasma level of GDNF in control and CRF groups. GDNF was not detected in plasma from any of the healthy controls. Although we tried to detect the plasma GDNF using a concentrating membrane filter system (Amicon Centricup, USA), which increases the detection limit of GDNF assay to 0.5 pg/ml, we failed to detect a significant level of GDNF in any of the control samples studied. In contrast, tests of plasma from CRF patients showed that GDNF was present in 53% (24/45) of samples studied, with a range of 2–38 pg/ml (average 7.8 pg/ml). Plasma GDNF levels in diabetic nephropathy, nephrosclerosis, and chronic glomerulonephritis were not significantly different (Mann–Whitney’s U test). The numbers of patients are listed in brackets.

Table 1. Plasma GDNF concentrations in patients with chronic renal failure and in controls. All values are mean ± SEM (pg/ml).

<table>
<thead>
<tr>
<th>GDNF (pg/ml)</th>
<th>Control (n=15)</th>
<th>Diabetic nephropathy (n=18)</th>
<th>Nephrosclerosis (n=11)</th>
<th>Chronic glomerulonephritis (n=16)</th>
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<tr>
<td>Chronic renal failure; total</td>
<td>7.8 ± 1.7</td>
<td>7.0 ± 2.5</td>
<td>7.7 ± 3.6</td>
<td>8.6 ± 3.1</td>
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Fig. 1. Correlations of plasma GDNF concentration with plasma TGF-beta-1 level in patients with CRF from diabetic nephropathy.