Systematic reviews and their roles in promoting evidence-based medicine in renal disease

D. Fouque¹, M. Laville¹, M. Haugh² and J. P. Boissel²

¹Département de Néphrologie, Hôpital Edouard Herriot; ²Département de Pharmacologie Clinique, Avenue Lacassagne, Lyon, France

How to obtain definite information from incomplete information

A systematic review of treatment proposed for a specific disease should be based on an exhaustive literature search, which should identify all randomized clinical trials (RCTs) relevant to the selected topic. Controlled non-randomized studies may also be included in situations where random allocation of treatment is deemed to be difficult or impossible, or when no such trials exist. If enough trials are found and these report conflicting results, a meta-analysis is one way of assessing the efficacy of the treatment.

Meta-analysis is a clinical research tool allowing the pooling of results from different clinical trials evaluating comparable treatments for a given condition. This is particularly useful when the number of patients is low, or the observed event rate is low. Meta-analyses can reduce the size of the confidence interval from the point estimate for the treatment effect. Thus if the treatment effect in each of three small trials shows a non-significant trend to efficacy, the pooling of the trials may result in a significant trend to efficacy. The selection of trials to be pooled, however, is an important step in a process that includes a rigorous statistical analysis (i.e. Mantel and Haenszel method). The choice of the outcome to be analysed should be based on strong epidemiological data or related to a clinically relevant question. Outcomes should be 'hard' objective events that are easily observed by non-specialists, such as death, recurrence of myocardial infarction, hospitalization. Data on at least one common outcome must be available in each trial [1,2]. In the renal field, an important event for patients, nephrologists and health care economists is the 'renal death' outcome, that we defined in 1992 as the occurrence of death, or the need to start chronic dialysis or to perform a kidney transplantation [3].

It is not uncommon that the outcome selected for a meta-analysis was not the main outcome reported in the individual trials. Sometimes the data for the outcome may not have been included in the clinical trial report. Hence, direct contacts with the investigators are mandatory to obtain data not previously reported and, importantly, also to verify the reported data. Lastly, more than one meta-analysis may be performed if physicians are faced with more than one clinically relevant question when managing the disease. Membranous nephropathy is one example in which data for a number of different outcomes have been recently 'meta-analysed': renal death, complete remission of proteinuria, improvement in proteinuria, impairment of renal function [4,5].

An epidemic of meta-analyses

The number of meta-analyses in psychology and medicine being reported over the last 20–30 years has increased enormously [6] and this number is now growing in the renal field. When we reported our meta-analysis of trials of low-protein diets in 1992 [3], there had only been one other meta-analysis in the renal field, published in 1988 [7]. A recent literature search has identified at least 34 published meta-analyses relevant to the renal field (Table 1), covering various aspects, e.g. radiocontrast nephrotoxicity [8] to long-term renal function after kidney donation [9]. As seen in Table 1, these reports have appeared in a number of medical journals that nephrologists probably do not read regularly. A database of randomized renal clinical trials and meta-analysis would therefore be useful for nephrologists. This could also help those designing new trials or those following on-going trials.

Scientific and medical progress regularly provides new evidence about existing treatments, and the importance of continual updating of systematic reviews to incorporate this new evidence has been recognized [10]. This has recently been illustrated in the renal field by the low-protein diet example. Low-protein diets have been prescribed during chronic renal failure for more than 30 years. At least 50 studies have been reported since 1975 and a meta-analysis has been recently published [3]. The incidence of renal death...
was found to be 17.6% in this meta-analysis, and it was suggested that a low-protein diet might reduce the incidence of death or the need to start dialysis as compared with the group receiving a larger protein intake [3]. More recently, the results from the Modification of Diet in Renal Disease (MDRD) study, in which the glomerular filtration rate decrease was used as an end-point were inconclusive [11]. The overall incidence of renal death in the MDRD study was similar to that found in our meta-analysis, i.e. 16.2% [11]. Updating the meta-analysis by adding the data for renal deaths observed in the MDRD study [12] strongly supports our findings, suggesting that reducing the protein intake during chronic renal failure delays the need to start dialysis (n=1413 patients, P=0.007).

### The important issue of end-points

Why should hard end-points be selected? Renal death (need to start maintenance dialysis or to receive a kidney transplant, although this is most frequently done after the start of dialysis) must include death of
patients, whatever the cause. Of course, there might be differences in criteria for starting dialysis between groups (and therefore between studies in the case of single-centre design). Random allocation of treatment is a mandatory design for selecting studies to be meta-analysed, in order to distribute identified or unknown biases which may interfere with the renal death criterion. One may argue that in the case of the low-protein diet, patients receiving a lower protein content will display lower serum urea and will need to start dialysis later on. However, a low protein intake may induce hyperkalaemia from increased vegetable content and induce a greater number of deaths in that group. It appears therefore that renal death still remains a robust epidemiological and methodological event.

One possible explanation for apparently conflicting conclusions between meta-analyses and the MDRD study could be the use of different outcomes, i.e. renal death in the meta-analyses and decrease in glomerular filtration rate in the clinical trial. Using intermediate (or possibly surrogate) end-points as secondary outcomes, such as decrease in glomerular filtration rate, can offer some advantages (e.g. often less expensive clinical trials) but this also presents some limitations [13]. The main limitation is the uncertain correlation between the surrogate endpoint and the clinical outcome. Thus, based on these observations, we strongly encourage investigators to use renal death as an outcome in any future trials on the progression of renal disease (although the decrease in glomerular filtration rate can be used as a secondary outcome). Furthermore, we suggest that the efficacy of low-protein diet has been, at least partly, demonstrated by the above results. Perhaps effort and funding could now be focused on the effects of new agents for protecting the kidney (i.e. angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, calcium-channel blockers, omega-3 fatty acids, etc.).

The most frequent criticism of meta-analysis is that of 'mixing oranges and apples' [14]. It should be stressed that a meta-analysis of data from 2000 patients does not have the same weight as a multicentre RCT including the same number of patients. Meta-analysis results enable a hypothesis to be formulated, and this should then be tested in a properly designed clinical trial; the results cannot be regarded as the highest level of medical evidence. In addition, not all meta-analyses are correctly performed, and some have a low level quality.

A proposal to promote a collaborative review group

The concepts necessary for evidence-based medicine have been developed through the work of various research teams throughout the world [15]. These concepts have been used to help set up a collaborative network, the Cochrane Collaboration, which was initiated in Oxford, UK, in response to the criticisms by Archie Cochrane, a British physician who was one of the pioneers who stressed the importance of applying conclusions from clinical trials to medical practice ('evidence-based medicine') [15-20]. The approach used in the perinatal domain [21] has been used as a model for developing collaborative review groups in other domains within the Cochrane Collaboration. We have been investigating the possibility for nephrologists to establish a similar group in their field, a Renal Review Group [22]. After three preliminary meetings, it seems that at least 50 nephrologists are interested in collaborating in such a group. The aims of this proposed Renal Review Group are: (1) to create and update a complete database of randomized renal clinical trials, (2) to perform and update systematic reviews pertinent to nephrologists, and (3) to provide information and advice to those designing future trials in the renal field. If you are interested, please contact Dr Denis Fouque at the address given on the title page.

Note added in proof

Reference [12] has been recently published as a full article: Ann Intern Med 1996; 124: 627–632

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