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

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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

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### Table 1. Non-exhaustive list of meta-analyses in the renal field

<table>
<thead>
<tr>
<th>Hypertension</th>
<th>Authors</th>
<th>Year</th>
<th>Journal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke, CHD, and BP (short-term reduction)</td>
<td>Collins</td>
<td>1990</td>
<td>Lancet</td>
</tr>
<tr>
<td>Stroke, CHD, and BP (prolonged reduction)</td>
<td>MacMahon</td>
<td>1990</td>
<td>Lancet</td>
</tr>
<tr>
<td>Fasting insulin and BP</td>
<td>Denker</td>
<td>1992</td>
<td>Arch Intern Med</td>
</tr>
<tr>
<td>Aspirin and pregnancy</td>
<td>Imperiale</td>
<td>1991</td>
<td>JAMA</td>
</tr>
<tr>
<td>Potassium supplementation</td>
<td>Capuccio</td>
<td>1991</td>
<td>J Hypertens</td>
</tr>
<tr>
<td>NSAIDs and BP</td>
<td>Pope</td>
<td>1993</td>
<td>Arch Intern Med</td>
</tr>
<tr>
<td>Thiazides and fractures</td>
<td>Jones</td>
<td>1995</td>
<td>J Bone Miner Res</td>
</tr>
<tr>
<td>Fish-oil and BP</td>
<td>Morris</td>
<td>1993</td>
<td>Circulation</td>
</tr>
<tr>
<td>Lipids and anti-HTN drugs</td>
<td>Kasiske</td>
<td>1995</td>
<td>Ann Intern Med</td>
</tr>
<tr>
<td>Calcium intake and BP</td>
<td>Capuccio</td>
<td>1995</td>
<td>Am J Epidemiol</td>
</tr>
</tbody>
</table>

| Acute renal failure (ARF)                                                    | Naylor        | 1988 | Renal Failure     |

| Contrast media and ARF                                                       | Barrett       | 1993 | Radiology         |

| Nephrolithiasis                                                              | Labrecque     | 1994 | Arch Intern Med   |

| Glomerulonephritis                                                           | Gansevoort    | 1995 | Nephrol Dial Transplant |
| Proteinuria and ACEI                                                        | Weidmann      | 1995 | ISN Madrid 1995     |
| Membranous nephropathy                                                       | Couchoud      | 1994 | Nephrol Dial Transplant |
| Membranous nephropathy                                                       | Hogan         | 1995 | Am J Kidney Dis    |
| Steroids and immunosuppressants (IgA)                                       | Imperiale     | 1995 | J Am Soc Nephrol   |
| Albuminuria and glomerular injury                                            | Schena        | 1990 | Nephrol Dial Transplant |
| Sepsis and central catheters                                                 | Perna         | 1996 | Am J Kidney Dis    |

| Haemodialysis                                                                | Jernigan      | 1993 | Ann Intern Med    |

| Transplantation                                                              | Kasiske       | 1993 | JAMA              |
| CsA withdrawal                                                              | Hricik         | 1993 | J Am Soc Nephrol  |

| Progression of renal failure                                                | Maki          | 1995 | Arch Intern Med   |
| Anti-HTN, renal function, and proteinuria                                   | Fouque        | 1992 | Br Med J          |
| Low vs control protein diet in adult CRF                                     | Kasiske       | 1993 | Ann Intern Med    |

| Pharmacology                                                                 | Keller        | 1993 | Clin Pharmacokinet |
| Neutlimic PK and renal function                                              | Massy         | 1995 | Kidney Int        |

| Urinary tract infection                                                      | Leibovici     | 1991 | Q J Med           |

| Single dose vs conventional antibiotics for UTI in women                     | Leibovici     | 1991 | Q J Med           |

| Miscellaneous                                                                | Kasiske       | 1995 | Kidney Int        |
can offer some advantages (e.g. often less expensive
comes, such as decrease in glomerular filtration rate,
death in the meta-analyses and decrease in glomerular
(or possibly surrogate) end-points as secondary out-
study could be the use of different outcomes, i.e. renal
conclusions between meta-analyses and the MDRD
the pioneers who stressed the importance of applying
cepts have been used to help set up a collaborative
have been developed through the work of various
proposal to promote a collaborative review group

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 con-
cepts have been used to help set up a collaborative
network, the Cochrane Collaboration, which was ini-
igated 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

Note added in proof

Reference [12] has been recently published as a full article: Ann

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309: 789–793
15. Boisell JP, on behalf of the Validata Group. The Validata
Group; a computerized system to deliver validated information

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 cri-
terion. 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 out-
comes, 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 out-
come. Thus, based on these observations, we strongly
courage investigators to use renal death as an out-
come 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.

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Meta-analyses in nephrology

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