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EDITORIAL COMMENT

RCT or not...

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Even large, well-conducted randomized controlled trials (RCT) can only reduce the area of uncertainty, not eliminate it. This assertion is supported by Adrian Covic's elegant discussion of recent studies in nephrology (1), which raised more questions than hard conclusions for current medical practice.

Science is the process designed to discover the truth, and "truth" is sampled each time a study is performed. The results of studies will be distributed around the "truth", depending on the questions asked, the chosen design, characteristics and size of samples. Hence, there are few chances to find "truth" based only on an individual study, even well designed and enough powered, but the probability increases with the number of appropriate trials.

Currently, the randomized controlled clinical trial is considered the ultimate test of a medical hypothesis, and is the support of evidence based medicine. According to certain criteria, a group of patients is assembled, randomly assigned to intervention and followed in real time for predefined end-points related to intervention. An alternative to RCT, is the observational approach, the prospective cohort study. A certain pre-defined end-point related to a certain intervention is evaluated prospectively or not, in a cohort of patients coming from "real life" medical practice. While "bias" are to be controlled in RCTs by selection of subjects, randomization and strict adherence to restrictive protocols, in the observational approach they should be overcome by an increase in number of observed subjects. Therefore, the strength of RCTs resides in control and randomization, whereas the force of observational studies comes from number.

Obviously, both ways to the "truth" depend on the accuracy of questions addressed.

The randomized controlled trials are useful to examine discrete interventions for carefully defined medical conditions. The more complex the patient population, the conditions or the interventions, the more difficult is to separate intervention effect from random variation.

To respond to the scientific rigor, a RCT must be designed to test a simple hypothesis. Therefore, the formulation of the hypothesis to be investigated is essential, as an inappropriate question can produce confusing answer, even using the best methods of investigation. For instance, anemia was unequivocally proved to be an independent predictor of death in renal patients, but its therapy failed to ameliorate prognosis or cardiovascular end-points in two recent large high quality RCTs, and controversies

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around hemoglobin target persist. It is well-known that anemia in renal patients is multifactorial, the sicker the patient, the lower the hemoglobin. The good question "Can anemia correction overcome the other conditions causing a low hemoglobin level (and high mortality and morbidity)?" would get the appropriate answer: probably not. It was not the case, and the RCTs answers are confusing.

Similarly, the risk of cardiovascular death is over ten times higher in renal patients than in the non-renal population within the same age group. In general population, the protective effect of statins is beyond doubt. In spite of these, a recent large RCT found no benefit of statins in renal population at highest risk for cardiovascular events, e.g. diabetics on chronic hemodialysis. Emerging data suggest that vascular disease is different in patients on renal replacement therapy. Thus, chronic volume overload, anemia, calcium-phosphorus and electrolytes imbalances, malnutrition impose a peculiar spectrum of risk factors. Although most of the mortality in these patients is considered to be of cardiovascular origin, in large series about one third of deaths is reported as "sudden death", which occurs mainly in the long inter-dialytic period, suggesting an important role of electrolytic disturbances rather than of the cardiac injury itself. Again, the good question "Can statins overcome the peculiar cardiovascular risk factors pattern in patients on renal replacement therapy?" would get the appropriate answer: probably not. Otherwise, the answer could be confusing.

Dialysis was a major advance in the medical therapy of renal failure. Although dialysis was based on precise physico-chemical principles and saved a lot of lives, more than fifty years after its introduction, we still use the small molecules clearance as a marker of efficacy, in spite of many data suggesting that small molecules, and especially urea, are not the best marker to be targeted. The good question "Is urea removal a marker of dialysis adequacy ?" was answered properly by RCTs: probably not.

On the other hand, in a RCT all supposed factors of confusion are to be mitigated. On this purpose, firm inclusion criteria are used, the intervention is addressed unequivocally to a condition and is strictly regulated by rigid protocols. Moreover, external monitoring is a prerequisite. As a result, RCT incur the risk to depict an artificial situation, which differs from the one seen in real medical practice. The recognized "study effect" is a well-fitted example of such a RCT limitation.

An additional difficulty in translating RCTs results in current practice is the induction. Even if several top-quality trials are available, questions about how far and to which populations their results are relevant always remain. Furthermore, skepticism may be extended to areas not explicitly covered by the trial. For instance, a certain intervention may be proved to influence an "intermediate end-point" such as blood pressure, glomerular filtration rate, cholesterol or hemoglobin level, without saying anything about "hard end-points" like cardiovascular events, patient or kidney death. The skeptics will demand to postpone the intervention until it can be shown to save lives.

A recent metaanalysis and an observational retrospective study rise questions about the efficacy of ACE inhibitors in preventing and slowing down the decline in renal function in chronic kidney disease (CKD) patients, as opposed to the plethora of literature proving the contrary. ACE inhibitors are drugs difficult to handle. When using them in the elderly, a population at higher risk of CKD, but also prone to renal vascular disease and volume depletion, the probability of hypotension or hyperkalemia would conceivably increase. In RCTs, exclusion criteria and careful monitoring would prevent such events, which is not probably the case in day to day practice and is mirrored by the mentioned papers.

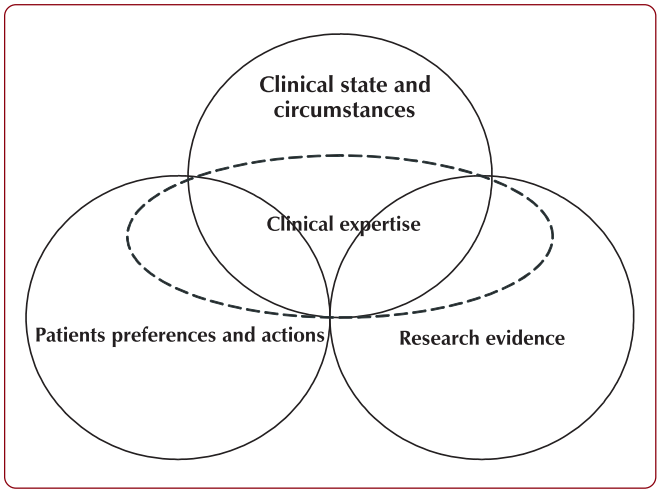
The financial burden is another problem of RCTs, as a RCT is costly. The scientific community must get financial support to perform a RCT, most of which comes from the industry. Even if we consider that the conflict of interest statements could solve part of the problem, the concern about pure scientific objectives is not uniformly distributed among industry representatives as is the willingness to allocate financial resources. That is to say that some drugs will be more prone to be evaluated in RCTs (and prescribed) than others.

These issues are not intended to diminish the central role detained by RCTs in evaluating interventions or defining regulatory criteria, all important in clinical medicine. However, the common belief that only RCTs produces gold standard evidence as opposed to observational studies could do a disservice to patient care, clinical investigation and to education of health

care professionals. We should recognize the potential problem we face, e.g. "*... the justification for why studies are included or excluded from the evidence base can rest on competing claims of methodologic authority that look little different from the traditional claims of medical authority that proponents of evidence-based medicine have criticized ... interpretative decisions by old pre-evidence-based medicine experts may be replaced by interpretative decisions from a new group of experts with evidence-based medicine credentials ...*" (2). We can identify here the opposition between "empirical trend", based on "experience" for cure of the sick and the "rationalistic trend" based on "mechanism and measure" of disease, old as medicine. A more balanced and scientifically justified approach is to evaluate the strengths and limitations of well done experimental and observational studies, recognizing the attributes of each method.

The randomized controlled study is not a gold standard. Merely, it is a good experimental design in some circumstance, but that's all. Thus, the limitations of RCTs could be overcome by the large-sized observational studies in founding good practice recommendations. The QUEST (QUality EUropean Studies) initiative of European Renal Association Registry launched by Carmine Zoccali is a good opportunity to gain data from the majority of European dialysis centres and to use them for large observational studies, like PRIMA (Protocol Intensified Multifactorial Approach) proposed by Christoph Wanner at second QUEST convention (march, 2006) and mentioned by Adrian Covic (1,5).

Recently, a group of authors developed a model for evidence-based decision making (3,4). Evidence-based decision making depends upon utilizing clinical expertise to integrate information about a patient's clinical setting and circumstances with the best research evidence whilst incorporating the patient's preferences and actions. The components of this model and the role of RCTs in evidence-based decision making are beyond the intention of these reflections, but what I intend to underline is the importance of clinical expertise. Clinical expertise is required to establish, balance and integrate the patient's clinical state and circumstances, preference and actions, and the best research evidence.



Model of evidence-based decision making

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