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For debate

Randomized controlled trials remain fundamental to clinical decision making in Type II diabetes mellitus: a comment to the debate on randomized controlled trials

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The role of RCTs in medical science

The introduction of the randomized controlled trial (RCT) to prove efficacy and safety of a treatment or superiority of new treatments over existing therapies was a cornerstone in the development of modern medicine. First described by Louis in 1850 [1] and implemented just over 100 years later by A. Bradford Hill [2], the RCT is an experimental approach to test a defined question while minimizing potential sources of bias and confounding. The results provided by RCTs are of a higher validity and contribute more to medical knowledge than traditional methods, such as the accumulation of clinical experience by experts, observational cohort, and case control studies. In clinial epidemiology, the RCT provides experimental evidence for the causes of the benefits and harms of a therapeutic intervention seen in patient-oriented outcomes. An international net of Cochrane Centres has been established to summarize the best evidence available by systematic reviews and meta-analyses. These reviews are continuously updated providing state-of-the-art information on therapies widely available to the medical community and to the public [3, 4].

Recently, RCTs have become the crucial element in the system of evidence-based medicine, which aims at identifying the "best evidence available" as a guide for clinical decision making for the individual patient [5]. This movement to focus routine clinical decision making on hard evidence is a response to a series of erroneous developments in medicine [6]. Popular therapeutic modalities have been arising without proof of their efficacy and safety. Repeatedly, these treatments have been shown to be useless or even harmful when appropriate evidence finally became available through RCTs directed at patient-oriented outcomes [7–10]. Other popular interventions, such as preventive hormone replacement therapy in postmenopausal women or treatment with anti-oxidants are still being carried out worldwide without any evidence of their efficacy and safety from appropriate RCTs. On the other hand, without RCTs the effectivness and safety of certain therapies could be overlooked [11].

Evaluation of therapeutic efficacy and safety are the domaine of RCTs

The lack of evidence for therapeutic interventions is particularly compelling in the care of Type II (non–insulin-dependet) diabetes mellitus. Thus, the innumerable "diabetes diets" and "nutrition prescriptions" that go beyond Bouchardat's basic rule "Mangez le moins possible" lack any scientific justification [12].

Worldwide an estimated 100 million people with Type II diabetes are treated with oral antidiabetic drugs. More than 100 000 reports on oral antidiabetic drugs have been listed in the Medline medical database since 1967. Only two studies have ever attempted, however, to address the basic question of whether blood glucose lowering therapies improve medium-term and long-term patient-oriented outcomes, such as the incidence of vascular complications, morbidity and mortality, using RCT methodology: the University Group Diabetes Program (UGDP) study [13] and the UKPDS [14].

Even though there had been some circumstantial evidence from observational studies of a causal rela-

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Abbreviations: RCT, Randomized controlled trial; GDP, University Group Diabetes Program; ADREP, any diabetes-related end point.

tion between hyperglycaemia and microangiopathy in Type II diabetes [15] and even hard evidence to this effect in Type I (insulin-dependent) diabetes mellitus [16], the UGDP and the UKPDS were crucial identifying causal relations as the basis of evidence-based clinical decision making [17].

Furthermore, due to its design as a RCT, the UKPDS was able to prove the safety and efficacy of intensive blood pressure control in preventing microvascular complications [18]. This was clinically an important finding which had not been expected from the observational data.

In both these RCTs there was no beneficial effect from lowering blood glucose on either the incidence or progression of macrovascular disease [13, 14]. In the UKPDS, intensive control of blood glucose [aiming at fasting plasma glucose of < 6.0 mmol/l (108 mg/dl); achieving a medium HbA_{1c} of 7.0% over 10 years] led to a reduction of the aggregate end point "any diabetes-related end point" (ADREP) from 46% to 41% and of "microangiopathy" from 11.4% to 8.6% when compared with conventional control of blood glucose [aiming at fasting plasma glucose < 15 mmol/l (270 mg/dl) and avoiding hyperglycaemia related symptoms; achieving a median HbA_{1c} value of 7.9% over 10 years] [14]. Such benefits were seen when glibenclamide or insulin were used as first line treatments for intensive control of blood glucose. With tolbutamide and chlorpropamide untoward side effects were, however, documented, such as an increase in cardiovascular mortality [19] and arterial blood pressure [14], respectively. In contrast, common expert interpretations suggest that the UKPDS calls primarily for a lowering of blood glucose, no matter by which oral antidiabetic drugs and by which polypharmacotherapy [20–22]. These experts rely, in making recommendations, on data from observational studies showing similar short-term improvements in glycaemia by a number of different drugs. The conclusions from such data contrast with the evidence available from RCTs. This evidence is, for efficacy and safety, against a so-called group effect of sulphonylureas and favours drug-specific profiles [23].

Should it be felt desirable to introduce the general use of sulphonylureas other than glibenclamide, their efficacy and safety must be proved by RCTs directed at patient-oriented outcomes. Before the general use of any new oral antidiabetic drug can be recommended, its superiority to (or at least aequipotency with) glibenclamide should be proved by end-point directed RCTs.

In addition, the need for conducting a RCT on the efficacy and safety of sulphonylurea drugs for Type II diabetic patients with coronary heart disease (CHD) has become obvious. Tolbutamide was shown to increase cardiovascular mortality in patients with Type II diabetes as early as 1970 [19], whereas glibenclamide and chlorpropamide were not associated with increased cardiovascular mortality in the UKPDS. Patients with clinically apparent coronary heart disease were, however, excluded from this study [24]. Data from animal experiments and from clinical research have provided arguments for the hypothesis that sulphonylurea is cardiotoxic in patients with CHD [25–27]. This hypothesis is compatible with the striking improvement in 3.5-years outcomes for these Type II diabetic patients who, after suffering acute myocardial infarction, received insulin therapy compared with those receiving standard therapies [28]. For the safety of millions of Type II diabetic patients with CHD treated with sulphonylureas either the imposition of a warning (like in the USA), a ban on their use in patients with coronary heart disease, or a decisive RCT seems mandatory. Observational cohort or case control studies cannot provide the data to refute or confirm this alarming hypothesis.

We have proposed a randomized controlled trial [Diabetes and Coronary Artery Disease (DICAD) Study] comparing total and cardiovascular mortality in Type II diabetic patients with coronary heart disease treated with either glibenclamide, glimepiride or insulin. After the extensive deliberation of a worldwide panel of about thirty experts the protocol was presented. According to current funding modalities, at least in central Europe, such a study would have to be sponsored by the company producing the respective drugs, i.e. in this case Hoechst-Marion-Roussel. After almost 3 years of tortuous discussions, the company declined to finance the trial even though the estimated costs of the study would have been minute compared with the company's expenditures in marketing these drugs, including the innumerable marketing studies restricted to the mere documentation of effects upon surrogate markers. On the other hand, to seek co-funding from several pharmaceutical companies seems unacceptable because, under the present circumstances, this would inevitably lead to amendments and enlargements of the study protocol, as were obviously imposed during the course of the UKPDS [29] which could result in "confounding by co-funding". We disagree with the contention that such a RCT would be impractical or too costly or both. Without one the millions of Type II diabetic patients with coronary heart disease currently being treated worldwide with sulphonylurea drugs are participants in an uncontrolled experiment, at best followed by observational methods, which will never shed any valid light on the potential cardiovascular risk they are being subjected to.

A recent report by Cornu et al. [30] on the safety of drugs already in worldwide use is an example of the alarming dependency on the pharmaceutical industry in the planning and execution of an RCT on the safety of their drugs.

In the early 1990s, a group of European scientists (EUTERP Pilot Study Group) attempted to set up a randomized controlled clinical trial to document efficacy and safety of hormone replacement therapy in post-menopausal women with 5-year total mortality as the primary end point. Ultimately, mainy because of the unwillingness of pharmaceutical industries to fund a RCT, the project had to be abandoned. Although millions of women are being treated with oestrogen/gestagens to prevent osteoporosis fractures and cardiovascular diseases (based on results from meta-analyses of cohort or case control studies) neither the efficacy nor safety of such preventive interventions have ever been proved. A recent RCT in postmenopausal women with coronary artery disease has shown an increased primary coronary event rate (i.e. aggregate end point of non-fatal myocardial infarction and coronary death) during the first year of such therapy without the documentation of any patient-oriented outcome benefit [31].

These are impressive examples of the need to conduct RCTs to document efficacy and safety for drugs which are already being widely used. Like Cornu et al. [30] we conclude from this frustrating experience that an impartial fund into which several parties make appropriate contributions must be created by a governmental (such as in the USA) or by a non-governmental institution to facilitate RCTs without depending on the goodwill and the marketing interests of the pharmaceutical industry.

Randomized controlled studies do have their limitations; they need to be interpreted carefully as discussed by Vijan et al. [32] and elswhere. To do so in a systematic fashion is advocated by evidence-based medicine which aims at only using the best available external evidence for an individual patient. Even if RCTs are available, their study design quite often fails to correspond exactly with the patient's individual situation. In such an instance, Sackett recommends that the physician, in making a clinical decision for and with the individual patient, examines whether there is anything against accepting at least part of the evidence available from randomized controlled trials [5]. Furthermore, the system of Sackett's evidence-based medicine allows for the presentation of data from complex RCTs by critical appraisal. As a result of lowering HbA_{1c} from a median value of 7.9% to that of 7.0% over 10 years, the UKPDS has shown an absolute risk reduction for ADREP by 5%, which corresponds to a number- needed-to-treat during 10 years ($NNT_{10\ years}$) of 20 (95% confidence interval 10–500). These data will assist the patients to decide which risk they are prepared to take and which efforts they are prepared to make in the long-term care of their Type II diabetes.

Need for additional RCTs

There remains a multitude of open questions of urgent clinical relevance to Type II diabetes which can only be solved through RCTs. These relate to the fundamental issues of efficacy and safety of therapeutic interventions, such as correction of hypertriglyceridaemia, hyperhomocysteinaemia or hyperinsulinaemia/insulin resistance, normalization of body weight, prolonged QT dispersion and hormone replacement therapy in postmenopausal women. No valid data are available for patient-oriented outcomes, effectiveness and safety for any oral antidiabetic drug, with the exception of glibenclamide and metformin. Further there are additional safety concerns for sulphonylurea and benzoic acid derivative drugs in Type II diabetic patients with CHD and the combination of metformin with sulphonylurea therapy. The concern over the safety of calcium antagonists in the treatment of hypertensive Type II diabetic patients is also still to be resolved [33, 34]. This cannot be done without a RCT which focusses on patient-oriented endpoints and directly compares antihypertensive agents with established benefit, such as cardioselective beta blockers and diuretics, with a calcium antagonist as first-line drugs. In the light of the worldwide popularity of calcium channel blocker drugs and the revenues accumulated from their use over the past decades, we strongly disagree with the widely held opinion that such RCTs would be too expensive to be fundable.

Observational studies are the domaine of quality assurance systems

Observational studies are indispensable for documenting the quality of health care and identifying center-to-center or physician-to-physician differences of outcome-oriented professional performance. Making use of the systematic aggregation of such data by benchmarking methods, improvements in outcome quality can be achieved based on quality circle techniques involving the respective health care providers [35–37].

Observational methods could also be used to describe certain sub-groups according to their specific risks. Within limitations such techniques, including simulation methods, could be useful to formulate cost-effectiveness analyses and to make general health care policies for screening procedures and individual therapeutic goals in specific sub-groups of Type II diabetic patients [31, 38, 39].

If data from RCTs are, however, analysed using observational methods, speculative conclusions could arise. The so-called "epidemiological analysis" [40] of the UKPDS data is an example. The information

from the UKPDS is limited in its experimentally achieved difference of glycaemic control over the 10-years study period (i.e. median Δ of 0.9% HbA_{1c} at values below HbA_{1c} 8.0%). The authors have attempted to overcome this limitation by epidemiological analyses. In contrast to the principle of a RCT, this method has an observational cohort analysis approach as used by J. Pirart [15] and others. It is inevitably subject to bias and confounding by, for example, an uneven distribution of relevant factors such as socio-economic status and the nature of the disease (C-peptide status, genetics etc.). It is obvious that those patients who manage to achieve ideal glycaemic ($HbA_{1c} < 6.5\%$) and blood pressure ($< 130/80$ mmHg) control throughout the study period differ in various ways from those who are less successful. Therefore, such epidemiological analyses of RCTs (also used by DCCT investigators, [41]) are of limited value. For the UKPDS data to calculate a hypothetical relative reduction for the 10-year incidence of ADREP or of microangiopathy for each per cent point of HbA_{1c} lowered seems fallacious.

Compared with RCTs, data from observational studies are of limited validity; they can, however, become useful within the framework of their limitations. Claude Bernard has extensively described the duality of "le méthode de l'observation comme médecine conjecturale et le méthode expérimentale comme médecine scientifique" [42]. Under certain circumstances, he suggested, that both approaches might be coordinated to advance medical knowledge as the basis of rational clinical decision making processes.

In principle, observational studies are the domaine of health care quality assessment. Thus, they are necessary to document the quality of health care given to diabetic patients by their health care providers. They are indispensable to show to which extent the evidence based on appropriate RCTs is being translated and implemented into routine clinical practice. It has been suggested that each diabetes centre should run continuous quality control assessments based on observational methods related to the patient-oriented outcomes of their patient care and should make these data public [43].

An important example of where this has been done is the PORT diabetes study [44] which documents that in a particular health care system, initiation of insulin therapy did not result in the intended improvement in metabolic control (even though it could well have resulted in an improvement of a primary patient-oriented outcome, i.e. hyperglycaemia related symptoms). This finding does not reflect on the efficacy and safety of insulin therapy but on the ability of a given medical care system and its health care providers to duplicate the performance in randomized controlled trials on insulin therapy, such as the UGDP ("insulin variable group") and UKPDS. Similar improvements in metabolic control upon the initiation of insulin therapy in unsatisfactorily controlled Type II diabetic patients on oral antidiabetic agents have been replicated by observational studies carried out under routine conditions of diabetes care in different health care systems [45, 46].

Conclusion

As an element of "la médecine expérimentale et scientifique" [42], RCTs remain fundamental in documenting efficacy and safety of therapeutic interventions. In Type II diabetes, a disturbing number of clinically relevant questions still await appropriate RCTs to ensure efficacy and safety of treatments currently extended to millions of patients worldwide. In principle, these issues cannot be resolved by consensus conferences between experts [47], observational approaches or studies directed to surrogate marker end points [48].

Given the availability of the experimental evidence from RCTs, observational studies and simulations could provide some additional insight on specific sub-groups of patients provided limitations due to potential confounding are taken into account. Observational studies, such as systematic benchmarking are indispensable and need to be carried out routinely to ensure that the quality of health care is compatible with success rates achievable elsewhere and, hence, that cost-effective care is offered to all diabetic patients in a given health care system.

As already proposed by Claude Bernard almost 150 years ago [42], experimental evidence (such as data from RCTs) and data from observational studies, (such as from cohort studies and simulation modelling) can complement each other to advance the quality of routine diabetes care provided in our various health care systems.

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