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Fifty years of type 2 diabetes clinical trials: a short review

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Abstract:

Background and Aim: Type 2 diabetes mellitus (T2D) is a global health concern, with more than 385 million people affected nowadays. Given its importance, many clinical trials were performed to evaluate aspects of this disease, especially the development and treatment of complications. The objective of this study is to elaborate a short review of the history, methodology, strengths and weakness of some major publications regarding T2D.

Methods: We selected and carefully analyzed five T2D clinical trials based on the suggestion of 5 experts in Brazil and Belgium.

Conclusion: In a time-line evolution, outcomes are becoming more objective. Recent trials have larger sample sizes with multiple recruiting centers and a successful attempt to avoid both random and systematic errors.

Key-Words: Diabetes mellitus type 2, clinical trials, short review.

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INTRODUCTION

Type 2 diabetes mellitus (T2D) is a global health concern, with more than 385 million people affected nowadays (1). This form corresponds approximately to 90- 95% of all diabetes and encompasses individuals with insulin resistance and usually relative insulin deficiency (2). The goal of the treatment is to prevent microvascular complications and cardiovascular events while avoiding side effects such as hypoglycemia. Due to its prevalence and severity, diabetes remains a major topic for several studies, ranging from small, specific trials, to large collaborative investigations (2,3). These characteristics make T2D one of the best examples of evidence-based practice in medicine.

The goal of this short review is to briefly describe the main characteristics of some important T2D clinical trials. Given that many of daily medical practices are based on these studies, the intention of this article is to give an idea of the history, methodology, strengths and weakness of the evidence regarding T2D.

Methods

We selected five major clinical trials involving T2D based on the suggestions of 5 experts from 3 teaching hospitals at our convenience - 2 in Brazil and 1 in Belgium. They were e-mailed asking to indicate, in their own opinion, papers they considered most relevant to their clinical practice and teaching. As there is a vast literature about T2D, more than 20 different articles were e-mailed back. Each article was carefully read and analyzed by the principal author and 5 were selected at his discretion, considering subjective criteria as historical importance, year of publication, the journal they were published and impact to current clinical practice.

Description

-Gottlieb B, Auld WHR (1962)

In 1962, Gottlieb et al. recruited 39 subjects to demonstrate that metformin was effective at treating diabetes (4). This trial did not include a control group and the sample was very heterogeneous - patients varied in regard to previous treatment response and etiology of the disease. The outcome was listed in levels of response to

metformin: “good, partial, failed or not assessed” which were poorly defined - based on symptoms, urinary glucose levels, and the need for insulin during the trial. Also, only age, weight, ketosis and previous use of insulin were described as baseline characteristics. Interestingly, there was no distinction between type 1 and type 2 diabetes, and the lack of response in individuals with less than 40 years of age led to the speculation that the drug could not work very well in young patients. Finally, there was no statistical analysis whatsoever. Despite its limitations, this paper has a valuable historical importance, as it was one of the first descriptions of the use of metformin for the treatment of diabetes in humans (4).

-UK Prospective Diabetes Study (UKPDS) Group (1998)

In 1998, UKPDS (United Kingdom Prospective Diabetes Study) released a large and complex trial – UKPDS 33. Much of our T2D knowledge comes from this group that started to work in 1977 and published many important

articles investigating complications and comparing T2D treatments. In UKPDS 33, newly diagnosed T2D patients were recruited and submitted to a complex randomization flow based on their body mass index. Non-overweight patients were randomized to receive insulin, sulfonylureas or conventional treatment with diet. Overweight patients could be assigned to another group – metformin intensive treatment. Conventional treatment subjects that developed marked hyperglycemia during the trial were posteriorly randomized to insulin or sulfonylurea. Twenty-one endpoints were predefined and included myocardial infarction, heart failure, amputation, renal failure, blindness and death. Glycated hemoglobin (HbA1c) was significantly lower in the insulin and sulfonylurea groups when compared to diet alone (7.0 vs 7.9%). Patients in the intensive group (HbA1c around 7%) had a lower incidence of the diabetes related combined endpoints, with a number-necessary to treat (NNT) of 19.6 over 10

Table 1: Summary of clinical trials

Year of publication Author	Primary Research Question	Design	Intervention and median follow-up	Control	Sample size	Outcome	Impact to current practice
1962 Gottlieb et al	Poorly defined. First look at the use of metformin in human subjects	Uncontrolled, one-arm clinical trial.	Metformin 6 months	None	39	Subjective – response to metformin	Use of metformin
1998 UKPDS-33	Is intensive pharmacological control more effective in controlling micro and macrovascular complications than dietary changes alone?	Randomized, nested clinical trial	Insulin or sulfonylurea 10 years	Diet	3041	21 clinical outcomes	Relationship between low HbA1c and better micro vascular outcomes
2002 DPP	Does a lifestyle intervention or treatment with metformin, a biguanide antihyperglycemic agent, prevent or delay the onset of diabetes? Do they differ in effectiveness or among demographical subgroups?	Randomized, three-arm clinical trial	Metformin or Intensive lifestyle modifications 2.8 years	Standard lifestyle modification + placebo	3867	Development of diabetes	Role of metformin and intensive lifestyle modification in preventing diabetes
2008 ACCORD	Is intensive therapy more effective in reducing major cardiovascular events in diabetic patients when compared to standard therapy?	Randomized, two-arm clinical trial	Intensive control (HbA1c ≤ 6.0%) 3.5 years	Standard control (7.0 ≤ HbA1c ≤ 7.9%)	10251	Combined non fatal stroke, non fatal myocardial infarction and cardiovascular death	Clinical relevance of microvascular benefits of diabetes' intensive control. Caution with hypoglycemia.
2008 ADVANCE	Is intensive therapy more effective in reducing major microvascular and macrovascular events in diabetic patients when compared to standard therapy?	Randomized, two-arm clinical trial	Intensive control using glizalide + drugs at discretion of assisting physician (HbA1c ≤ 6.5%) 5 years	Standard control not using glizalide	11140	Combined major and microvascular complications	Idea of individualized HbA1c target.

UKPDS: United Kingdom Prospective Diabetes Study; DPP: Diabetes Prevention Program; ACCORD: Action to Control Cardiovascular Risk in Diabetes Study Group; ADVANCE: Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation

years to avoid at least one endpoint, when compared to diet alone. This was mostly composed of a reduction in microvascular events (25% risk reduction, $p=0.0099$), while there was no significant difference in macrovascular events such as myocardial infarction ($p=0.052$), stroke ($p=0.52$) and amputation or death from perivascular disease ($p=0.15$) (5).

-Diabetes Prevention Program Research Group (2002)

In 2002, the Diabetes Prevention Program Research Group released the first article testing a drug to prevent T2D. In this multicentric 3-arm trial, pre-diabetes progression to diabetes was evaluated with standard lifestyle recommendations plus metformin at a dose of 850 mg twice daily, standard lifestyle recommendations plus placebo twice daily or an intensive program of lifestyle modification. The intensive lifestyle modification group had many assignments as reduction and maintenance of at least 7% of the weight, at least 150 min/week of physical activity and 16 lessons along 24 weeks covering diet, exercise and behavior. The standard lifestyle modification group had annually sessions of 20-30 minutes emphasizing the importance of healthy diet, physical activity and weight loss. Randomization was stratified by center and assignment to metformin or placebo was double-blinded. This trial was finished one year earlier than expected, with 65% of the planned person-years observations, after achieving statistical significance for superiority in pre-defined interim analyses, with corrected P-values. Yearly progression to diabetes was 58% lower in the intensive lifestyle modification group and 31% in the metformin group, both compared to placebo. As the trial was stopped early due to ethical concerns, it is difficult to infer the long-term effects of the proposed measures and the real progression rates to diabetes in each group. However, the results were robust enough to point to a benefit of either intensive lifestyle modifications or the use of metformin in the incidence of T2D (6). June 12, 2008. In the same issue of the New England Journal of Medicine, two large, high powered, controlled trials were published with apparent contradictory results – ADVANCE and ACCORD (7,8).

-ACCORD Study Group (2008)

ACCORD was designed to demonstrate the potential benefit of intensive glucose control in major vascular outcomes. All 10251 patients were randomized to different targets of HbA1c (below 6.0% vs 7-7.9%) using drugs at the discretion of investigators and patients. The primary outcome was a combination of macrovascular complications: non-fatal stroke, non-fatal myocardial infarction and cardiovascular death. Statistics were thoroughly described in this article, including the correction for multiple analyses. ACCORD was finished

earlier due to an unexpected increase in all cause death in the intensive control group (4.0% vs 3.0%, $P: 0.04$). Hypoglycemia was much more common in this group (16.2% vs 5.1%, $P<0.001$) and more classes of drugs were used with higher doses, leading to speculations about the cause of these deaths (7).

-ADVANCE Collaborative Group (2008)

The ADVANCE trial also compared intensive versus standard glucose control in T2D treatment, but with several differences from ACCORD. Gliclazide (a second generation sulfonylurea) was used in the intensive group while patients in the standard group were required not to use this medication; HbA1c target in the intensive control group was $\leq 6.5\%$; standard treatment HbA1c target was not predefined, remaining to the discretion of the attending physician. The primary outcome was combined macro and microvascular complications, which happened in 18.1% of the intensive glucose control group and 20.0% in the standard one ($P: 0.01$), with a NNT of 52 patients to avoid 1 of the combined primaries outcomes in 5 years (8).

Explanations for the apparent contradiction are numerous: results in the intensive group of ADVANCE were better because of microvascular benefits (not addressed in the ACCORD); HbA1c target was lower and hypoglycemia was much more common in ACCORD; gliclazide was part of the intervention in ADVANCE, but not in ACCORD. The lesson was that low levels of HbA1c prevent microvascular complications, but, especially when associated with multiple drugs, the high rate of secondary hypoglycemia can lead to higher short-term death rates (7,8).

DISCUSSION

The purpose of this article is to provide a short overview on some landmarks on the treatment of T2D, focusing mainly on the methodological differences and the practice changing impacts. Due to space and method limitations, it does not intend to be a full comprehensive review, but to provide an idea of what changed in 53 years of the studies on T2D.

There are many differences between how T2D trials were designed throughout the years. It's easy to note that outcomes are becoming more objective, defining primary and secondary outcomes, facilitating interpretation, and avoiding both systematic and random errors (type I and type II). On the other hand, medications to achieve a target of HbA1c are frequently used at the discretion of physicians and many different outcomes are evaluated, which can lead to apparent contradictory results (7,8). The sample size and the number of centers involved in the

studies are enlarging, improving the external validity (2-8).

As T2D has a slow evolution, the need for long-lasting trials is a big challenge, and brings problems such as loss to follow up and financial issues. Even though it is not the state-of-the-art endpoint, surrogate outcomes are often used as a way to address these issues, especially in smaller trials (2). Meanwhile large group initiatives sometimes provide us with the long, clinically based trials that give major base to current guidelines (5,7,8).

T2D has a vast literature available but physicians are still faced with many questions, especially of what drug to use and what HbA1c to target (3). With the recent development of new drugs with potential safer profiles (i.e. less hypoglycemia), while allowing for better glycemic control (2), there's still a lot to be studied, in a constant attempt to keep improving patient's survival and quality of life.

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