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Letter to the Editor

Looking for safety but overlooking efficacy: Non-inferiority trials of anti-diabetics

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To the Editor-in-Chief,

Testing new interventions against placebo when effective treatments are already available is considered unethical [1] and dangerous for patients [2], so testing non-inferiority which aims at demonstrating that a new intervention is not unacceptably worse than standard clinical practice should be equally unethical [3,4]. The understanding is that part of the benefit can be given up in exchange for less important advantages – such as better tolerability, convenience, etc. – which are claimed though often not proved. Going one step further, i.e. exploring even whether a treatment is non-inferior to placebo – meaning not unacceptably worse than doing nothing - should be inconceivable from both the ethical and the clinical points of view. Nevertheless, the approach has gained ground, for example in the area of diabetes.

From an anti-diabetic treatment one would expect a reduction of events involving the heart, peripheral vessels and nerves, kidney or eyes. However, cardiovascular events may be associated with both diabetes and some of its treatments [5]. Nonetheless, it is still surprising that clinical trials are often aimed at showing that anti-diabetic medicines do not cause any increase in major cardiovascular events and even more, “that the therapy [does] not result in an unacceptable increase in cardiovascular risk”. This is what a 2008 FDA guidance [6] stated and may have triggered a burst of so-called non-inferiority safety trials intended to show that a new anti-diabetic medicine is not (much) more harmful than placebo. We describe a couple of recent sample cases [7–9] which follow several others in the last decade.

The DECLARE–TIMI 58 trial [7] followed more than 17,000 patients with type 2 diabetes and high cardiovascular risk for about four years to test the hypothesis that dapagliflozin (a selective inhibitor of sodium-glucose co-transporter 2) does not raise the relative risk of major adverse cardiovascular events seen with placebo (cardiovascular death, myocardial infarction, or ischemic stroke) by more than 30%. Dapagliflozin did not affect the rate of cardiovascular events (8.8% in the dapagliflozin group and 9.4% in the placebo group; hazard ratio, 0.93; 95% CI 0.84-0.03); however, it did result in a lower rate of cardiovascular deaths or hospitalization for heart failure (4.9% vs. 5.8%; hazard ratio, 0.83; 95% CI 0.73-0.95), which was a co-primary outcome measure. In essence, the scant outcome of the trial was that dapagliflozin was not effective but at least did not harm patients by causing more heart failures. In any case, according to the non-inferiority hypothesis and the 30% margin selected, the investigators would have taken the results as good even if major cardiovascular events had occurred – say - in 120 every 1000 patients treated with dapagliflozin instead of the 94 given placebo. The question is: in exchange for what? Adequate glycemic control?

The CARMELINA trial [8] tested the same hypothesis in almost 7000 patients treated with linagliptin (a dipeptidyl peptidase-4 inhibitor) and followed for about two years. Luckily, here too the investigators did not see the 30% excess of events they were ready to consider acceptable: major cardiovascular events occurred in 12.4% and 12.1% patients respectively in the linagliptin and placebo groups (hazard ratio, 1.02; 95% CI 0.89-1.17). A secondary analysis [9] reported that linagliptin did not even affect the incidence of cardiovascular deaths or hospitalization for heart failure (11.6% compared to 12.1% in the placebo arm; hazard ratio, 0.94; 95% CI 0.82-1.08). In short, like dapaglifozin, linagliptin proved ineffective but harmless.

One first question relates to the trial hypothesis itself. Why should we accept any increase of the cardiovascular events we expect to reduce? This is even more surprising since that expectation is evidence-based: older anti-diabetics (metformin, sulfonylureas, insulin) and a few of the newer ones (empagliflozin, canaglifozin and liraglutide) have already been proved to prevent cardiovascular events, besides ensuring glycemic control. [10] The purpose of trials of new anti-diabetics should rather be to explore whether potentially innovative treatments further reduce cardiovascular risk besides controlling glycemia. However, if we assume that glycemic control is a valid surrogate of cardiovascular benefit for any other anti-hyperglycemic treatments – which is questioned [11] - we should expect a reduction of events, not an increase. Instead, regulators suggest – and clinical investigators adopt - an asymmetric evaluation of the efficacy and safety of anti-diabetics, the former relying on glycemic control, the latter on an acceptable increase in cardiovascular risk. This implies that a reduction of blood glucose is supposed by itself to counterbalance a possible higher incidence of cardiovascular events. Not to mention that the permitted

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higher incidence means up to 30% more major cardiovascular events than might be expected with placebo.

Not even the concern about cardiovascular events such as heart failure [5,9] should make clinical investigators satisfied with any excess of major cardiovascular events, however limited, particularly in the absence of evidence of clinical efficacy. Patients would not be happy to have more heart failure episodes – however few - if, despite their perfect glycemia, their risk of myocardial infarction or cerebral stroke or even of dying was no lower. Patients want to be sure they will have fewer major cardiovascular events overall, preferably without or with only a few heart failure episodes. To address this expectation clinical trials should assess how many major cardiovascular events a given anti-diabetic avoids, without increasing the heart failure rate. This implies a superiority test addressing the efficacy of an anti-diabetic intervention in reducing a composite outcome which encompasses major cardiovascular events including heart failure, not just a questionable excess over placebo.

An explicit conclusion of current trials of anti-diabetics should recognize that, at best, those trials proved the experimental drugs did nothing, i.e. were no more effective than placebo, but hopefully with no worse toxicity - which is what non-inferiority versus placebo actually implies. It is disappointing that clinical investigators and ethics committees from so many clinical sites in different countries agreed on this scant outcome after involving so many patients for so long. Potential participants would certainly deny their consent if adequately informed about the scope of trials intended to show that new anti-diabetics are possibly not (very) harmful, though not necessarily beneficial.

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Declaration of Competing Interest

None.

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References

[1] World Medical Association. The Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects. 2013https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/, Accessed date: 15 April 2019.
[2] Garattini S, Bertele' V, Banzi R. Placebo? No thanks, it might be bad for me!. Eur J Clin Pharmacol 2013;69:711–4. https://doi.org/10.1007/s00228-012-1383-6.
[3] Garattini S, Bertele' V. Non-inferiority trials are unethical because they disregard patients' interests. Lancet 2007;370:1875–7. https://doi.org/10.1016/S0140-6736(07)61604-3.
[4] Bertele' V, Banzi R, Gluud C, Garattini S. EMA's reflection on placebo does not reflect patients' interests. Eur J Clin Pharmacol 2012;68:877–9. https://doi.org/10.1007/s00228-011-1175-4.
[5] Zannad F, Rossignol P. Dipeptidyl Peptidase-4 inhibitors and the risk of heart failure regression to the truth? Circulation 2019;139:362–5. https://doi.org/10.1161/CIRCULATIONAHA.118.038399.
[6] Food and Drug Administration. Guidance for Industry—Diabetes Mellitus Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/UCM071627.pdf, Accessed date: 15 April 2019.
[7] Wiviott SD, Raz I, Bonaca MP, et al. DECLARE–TIMI 58 investigators. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2019;380:347–57. https://doi.org/10.1056/NEJMoa1812389.
[8] Rosenstock J, Perkovic V, Johansen OE, et al. Effect of Linagliptin vs placebo on major cardiovascular events in adults with type 2 diabetes and high cardiovascular and renal risk. The CARMELINA randomized clinical trial. JAMA 2019;321:69–79. https://doi.org/10.1001/jama.2018.18269.
[9] McGuire DK, Alexander JH, Johansen OE, et al. CARMELINA Investigators. Linagliptin effects on heart failure and related outcomes in individuals with type 2 diabetes mellitus at high cardiovascular and renal risk in CARMELINA. Circulation 2019;139:351–61. https://doi.org/10.1161/CIRCULATIONAHA.118.038352.
[10] National Institute for Health and Care Excellence. Advice: Type 2 Diabetes Mellitus: Medicines Optimisation Priorities. https://www.nice.org.uk/advice/ktt12; 15 January, 2015, Accessed date: 15 April 2019.
[11] Rodriguez-Gutierrez R, McCoy RG. Measuring What Matters in Diabetes. JAMA 2019;321:1865–6. https://doi.org/10.1001/jama.2019.4310.

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