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Cardiologist and Diabetologist crosstalk in the era of cardiovascular outcome trials of novel glucose-lowering drugs

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ABSTRACT

The prevalence of type 2 diabetes continues to increase and cardiovascular (CV) diseases remain the leading cause of death in diabetic patients. Diabetologists and Cardiologists have to work together in order to provide the best management to these patients. After years of disappointing studies showing no reduction of CV events with strict glycaemic control, some of the novel glucose-lowering drugs (GLDs) seem to offer a new approach to tackle the problem, since the CV outcome trials (CVOTs-D) of liraglutide, semaglutide, empagliflozin and canagliflozin have demonstrated not only their CV safety but also their efficacy in the reduction of CV morbidity and mortality. Along with the initial enthusiasm, concerns have been raised about the economical sustainability of long-term therapies considering higher costs of new molecules relative to the traditional ones. As expenses in the medical field are on the rise, healthcare systems need to balance the positive impact of an intervention and its overall cost. This review is meant to offer the Cardiologists a different point of view on the positive influence of GLDs, in the light of the main trials in the CV fields they are familiar with. The purpose of this article is to critically review the magnitude of the CVOTs-D results by the analysis of their statistical determinants, to establish the extent of the GLDs positive impact on patients with both diabetes and CV disease. The analysis has been performed taking into account models and statistical determinants used in the main landmark cardiology trials. It is fundamental to translate the result of CVOTs-D in clinical practice: the interdisciplinary crosstalk between the Cardiologist and Diabetologist is of paramount importance in order to fully exploit the power of the new available pharmacological strategies.

1. Introduction

The crosstalk between Cardiology and Diabetology has never been so intense as after the emergence of the recent evidences that might radically change the way diabetic patients are treated. Recent epidemiological studies confirmed the increasing burden of patients with both type 2 diabetes and CV diseases as the population age and comorbidities rise [1,2]. CV diseases remain the leading cause of death among people with diabetes [3,4], thus their management requires a multidisciplinary approach that goes beyond glycaemic control. Some of the new cardiovascular outcome trials in diabetes (CVOTs-D) on glucose-lowering drugs (GLDs) are at the foundation of a potential revolution with the demonstration of a significant reduction of major adverse CV events (MACE) and mortality. Along with the great interest for the positive results, issues have emerged regarding the applicability and cost-benefit of these drugs in everyday clinical practice. CVOTs-D and CV trials, despite differences concerning study population and interventions, share some common features in terms of methodology, design and primary endpoints. This review will critically analyse the magnitude of the CVOTs-D results, by means of a detailed evaluation of the statistical determinants that made the difference in the main CV trials. The comparison of recent CVOTs-D to CV trials that had great impact on patients' outcome may lead to the identification of major benchmark parameters that guarantee the extent of the positive effect of novel GLDs. The trials on new glucose-lowering drugs observed with the proper light, with the support of a robust statistical basis and with focusing on the whole CV panorama can reveal new interesting therapeutic tools Cardiologists and Diabetologists should share to achieve the best treatment of their common patients.

2. A change in the field of diabetes care

Coronary artery disease is responsible for as many as 30% deaths in the diabetic population [5] and more than two thirds of diabetic patients aged 65 years or older die because of vascular problems [4]. Notably, silent ischemia is known to be far more prevalent in diabetic than in non-diabetic patients (10–20% vs 1–4%) [6].

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The most controversial point in diabetes care is the discrepancy between data that show a clear increase of the CV events risk with worse glycaemic control and interventional studies which did not find a consistent association between reduction of glycated haemoglobin and reduction of CV disease [7]. A strict control of glycaemia did not consistently show to reduce either mortality or the macrovascular complications of diabetes. On the other hand, it seems to be beneficial for microvascular complications, certainly with the negative counterpart of an increased amount of severe adverse events, such as hypoglycaemias and weight gain [8]. Several reasons may account for these disappointing results and the key one is the multifactorial basis of the CV risk in type 2 diabetes [9]. The growing awareness of the CV complexity of the diabetic patient requires moving towards a complete multidisciplinary approach, with Diabetologists and Cardiologists working together and with other specialists (e.g. Nephrologists), and emphasizes the role of GLDs, able not only to reduce blood glucose, but also to positively modify the global CV risk of the patient.

In 2008 the Food and Drug Administration (FDA) introduced the requirement of investigating the CV outcomes of new glucose-lowering medications for the sake of safety [10]. This need stemmed from the results presented in the 2007 on rosiglitazone [11], which suggested an increased risk of myocardial infarction and of death from cardiovascular causes with the use of this PPAR-gamma agonist. Since then, several CVOTs-D have been conducted and, even if they were introduced primarily to demonstrate the cardiovascular safety of new anti-diabetic agents looking for approval, some of them revealed an impressive impact on CV outcomes.

In the last years, Diabetologists have seen the introduction of various classes of GLDs in addition to the traditional well-known medications: dipeptidyl peptidase-4 (DPP-4) inhibitors (e.g. saxagliptin, sitagliptin), glucagon-like peptide 1 (GLP-1) receptor agonists (e.g. liraglutide and semaglutide) and sodium-glucose co-transporter (SGLT)-2 inhibitors (e.g. empagliflozin and canagliflozin). The pre-clinical data and clinical findings on the cardiovascular effects of these GLDs have been extensively reviewed elsewhere and the results of the main studies have been largely presented, further analysed and deeply debated. In particular, the EMPA-REG OUTCOME trial [12], the LEADER trial [13], the SUSTAIN-6 trial [14] and the CANVAS-program [15] have shown superiority of empagliflozin, liraglutide, semaglutide and canagliflozin, respectively, on the 3-point MACE outcome (cardiovascular death, non-fatal myocardial infarction or stroke) (Table 1). The strength of the data obtained by the latest trial prompted a revision of the positioning of these GLDs in the current treatment algorithm of type 2 diabetes, in particular in patients with higher CV risk, and changes have already been made in the guidelines of some scientific societies [16–19].

3. Concerns and doubts

As always when important changes to the present clinical management are proposed, doubts and questions come along with the enthusiasm following the publications of the trials. Some important points of discussion regard the pathophysiological mechanisms at the base of the positive outcome results, the role of these treatments in different populations (e.g. at lower CV risk), the possible existence of a drug class effect, the economic issues due to high costs of GLDs and the relatively short median follow-ups of the trials.

Previous drugs were able to obtain optimal glycaemic control but without any positive effect on CV mortality. The pathophysiological mechanisms that may explain why GLDs can yield such a reduction in the CV outcomes are still unclear. Useful considerations have already been proposed for some classes of drugs by several authors. In case of SGLT2 inhibitors, the mechanism seems the renal handling of both sodium and glucose that favours osmotic diuresis causing hemodynamic changes, favourable in modifying heart failure natural history [20–22]. On the other hand, for other classes of drugs, the reasons for such impact are not obvious and are still under evaluation, prompting further research.

Certainly, it is not possible to directly extend the findings to the whole population of patients with diabetes. Study populations vary largely in terms of characteristics and in terms of overall number of enrolled patients. Trials often include patients at high risk of CV events in order to provide an adequate number of events in a relatively short period of time. As a result, current CVOTs-D are not representative of the larger population. For example, the role of drugs such as empagliflozin seems to be strong in high CV risk diabetic patients, while their role in low risk patients is not clear. Moreover, primary composite end-points might bear slight differences that warrant attention if comparison about effects and individual outcomes should be made.

The actual design of CVOTs-D presents limitations regarding short median follow-ups, as trials last <5 years. This relatively short timeline does not allow to detect some potential benefits, because they may take years to become apparent, as natural history of diabetes and CVD has a long development timeline. In the same way, potential serious harm coming from these drugs can be masked by short follow-ups, as side effects may require years of treatment to become recognizable, especially in case of agents with complex multiple mechanisms of action.

Issues have been raised regarding the increasing cost of diabetes care [23,24] and concerning the economical sustainability of these drugs and their use in everyday clinical practice [25]. Problems have arisen from the higher unitary cost of new molecules relative to the traditional ones. This is an almost constant problem that physicians have to face with at the introduction of new therapies, as recent advances in cardiovascular pharmacotherapy demonstrate (e.g. introduction of direct oral anti-coagulants or, even so more, of PCSK9 inhibitors). Healthcare systems always require balancing the need for prevention and adequate treatment with a real positive impact not only on individual outcomes but also on the costs for the health system. This kind of

Table 1
Glucose-lowering drug cardiovascular outcome trials.

Study (ref.) year	Study drug	N. total	N. study drug	N. control	Primary endpoint	HR (95% CI)	RR (95% CI)[a]	ARR	NNT	Median follow-up
EMPA-REG OUTCOME [12] 2015	Empagliflozin Vs Placebo	7020	4687	2333	Death from cardiovascular causes, non-fatal myocardial infarction, non-fatal stroke	0.86 [0.74–0.99]	0.86 [0.75–0.99]	1.6%	61	3.1 years
LEADER [13] 2016	Liraglutide Vs Placebo	9340	4668	4672	Death from cardiovascular causes, non-fatal myocardial infarction, non-fatal stroke	0.87 [0.78–0.97]	0.87 [0.79–0.97]	1.8%	55	3.8 years
SUSTAIN-6 [14] 2016	Semaglutide Vs Placebo	3297	826 (0.5 mg) 822 (1.0 mg) Total 1648	1649	Death from cardiovascular causes, non-fatal myocardial infarction, non-fatal stroke	0.74 [0.58–0.95]	0.74 [0.58–0.94]	2.3%	43	2.1 years
CANVAS [15] 2017	Canagliflozin Vs Placebo	10142	5795	4347	Death from cardiovascular causes, non-fatal myocardial infarction, non-fatal stroke	0.86 [0.75–0.97]	0.84 [0.75–0.95]	1.7%	59	3.6 years

[a] Calculated from the number of events and the sample size, not reported in the original publications.

considerations is always very complex and the differences between the trials, lacking direct comparisons, make impossible drawing a definite conclusion.

The arrival of new GLDs have been observed with strong interest also by the Cardiologists and, together with these points of discussion, has stimulated a spontaneous comparison with the trials they are familiar with into the CV arena. Therefore, the main landmark cardiology trials can be used as models to shed light on CVOTs-D and to review the magnitude of the GLDs positive results with the support of the main statistical parameters derived from the trials. The ensuing paragraphs revise the main indices useful in trial critical interpretation that may help for in-depth considerations on CVOTs-D and CV studies.

4. Tools in the evidence-based era: measures of association and measures of effect

The clinician's ability to critically appraise trials is an essential skill in the evidence-based medicine era. The CONSORT statement [26] for reporting of results of clinical trials recommends specific parameters to be reported. The tools offered by statisticians can be very helpful as they allow to critically understand scientific evidences and to make adequate comparisons. Several indices exist in order to study the association of an exposure and an outcome and to quantify the effect size of an intervention; Table 2 shows a concise overview of the most important ones. All the parameters have their own particular limitations not to be forgotten.

Two measures help in defining the association between an exposure and an outcome:

- The risk is the ratio between the chance of the outcome of interest to occur and all the possible outcomes;
- The term odds refers to the ratio between the probability of occurrence of the event and the probability of the event not occurring.

From these measures, the relative risk (RR) and odds ratio (OR) can be computed. They describe the magnitude of the difference in risk or odds for the occurrence of an event between the group that is exposed and the group that is not exposed to a certain intervention (Table 2).

In the following section, RR, absolute risk reduction (ARR), relative risk reduction (RRR), hazard ratio (HR) and number needed to treat (NNT) will be described, as they are the most commonly indexes encountered in trials.

The RR (or risk ratio) is calculated as the ratio of the risk of an event in the exposed group versus the risk of the event in the unexposed group [27,28]. It is commonly employed in prospective studies (cohort

Table 2
Main statistical indices in evidence-based medicine trials.

Measures of association		
RISK	R = N° events of interest / total N° events	Represents the probability of an outcome to occur. It is the ratio between the chance of the outcome of interest to occur and all the possible outcomes.
ODDS	O = p / (1 – p)	The ratio between the probability of occurrence of the event and the probability of the event not occurring.
RELATIVE RISK (RR)	RR = risk of event in exposed group / risk of event in unexposed group.	Ratio of the risk of an event in the exposed group to the risk of the event in the unexposed group. - RR = 1 no difference between the two groups; - RR < 1 event less likely to occur in exposed group; - RR > 1 event more likely to occur in exposed group. RR can be calculated in prospective studies (cohort studies) where the total number of exposed people is available.
ODDS RATIO (OR)	OR = odds of event in group 1 / odds of event in group 2	Ratio of the odds of a certain event in one group to the odds in the other group. - OR = 1 no difference in risk between the two groups; - OR < 1 event less likely to occur in exposed group; - OR > 1 event more likely to occur in exposed group. In retrospective (case-control) studies, where the total number of exposed people is not available, RR cannot be calculated and OR is used as a measure of the strength of association between exposure and outcome. In prospective cohort studies, where the number at risk (number exposed) is available, either RR or OR can be calculated. Multiple logistic regression, a frequently used multivariate technique, calculates adjusted ORs and not RRs.
Measures of effect		
ABSOLUTE RISK (AR)	AR = event rate in group X / total N° in group X	Represents the probability of a certain outcome in a population.
ABSOLUTE RISK REDUCTION (ARR)	ARR = AR in control group – AR in treatment group	Difference between the event rate in the non-exposed/control group and the event rate in the exposed/treatment group.
RELATIVE RISK REDUCTION (RRR)	RRR = ARR / event rate in control group or RRR = 1 – RR	Ratio between the absolute risk reduction (ARR) and the event rate in the non-exposed/control group. Represents the proportion by which the treatment reduces the event rate.
NUMBER NEEDED TO TREAT (NNT)	NNT = 1 / ARR	Reciprocal of the absolute risk reduction (ARR) in case of a positive outcome. Used in studies evaluating the effect of an intervention/treatment. Represents the number of patients to be treated in order to observe the outcome of interest. The smaller the NNT, the stronger the effect of the treatment.
NUMBER NEEDED TO HARM (NNH)	NNH = 1 / ARR	Reciprocal of the absolute risk reduction (ARR) in case of adverse event. Used in studies evaluating the effect of risk factor exposure/intervention. Represents the number of patients to be exposed/treated in order to observe the studied adverse event. The smaller the NNH, the stronger the risk factor effect.
Others		
HAZARD RATIO (HR)	HR = hazard* in treatment group / hazard* in control group. *Hazard calculation: $H(t): \lim_{\Delta t \to 0} \left(\frac{events\ in\ interval\ (t)/N\ at\ risk\ (t)}{\Delta t} \right)$	Represents the instantaneous risk, which means the probability an individual would experience the event at any fixed time point. Differs from OR and RR as they are cumulative over the entire study. Used in time-to-event analysis and survival analysis. - HR = 1 no difference in outcome between the two groups; - HR < 1 event less likely to occur in exposed/treatment group; - HR > 1 event more likely to occur in exposed/treatment group.

studies) where the number at risk is available. Notably, it describes the cumulative risk over the entire period of observation being calculated at the end of the study.

The ARR is the difference between the event rate in the control group and the event rate in the interventional group. Each event rate (i.e. the absolute risk) is the ratio between the number of events in that group and the total number of subjects in the group. ARR has to be interpreted in the context of baseline risk.

The RRR is the ratio between the ARR and the baseline risk in the control group. RRR is an estimate of the percentage of baseline risk that is removed as result of the new therapy and obviously requires the knowledge of the event rate in the control group: it is evident that a particular RRR may imply very different ARRs, depending on baseline risk.

The NNT is a widely used index that is frequently employed to report the results of trials [29,30]. NNT tells us the number of patients who would need to be treated with the new treatment rather than the placebo (or alternative therapy) for one additional patient to benefit (i.e. in order to reduce by one the number of patients experiencing the studied outcome). It is calculated as 1 divided by the ARR. The NNT is always considered a more "practical" measure, easy to interpret clinically, but has some limits. Due to its mathematical derivation, NNT varies also depending on the ARR. Thus, ARR value is important to consider when interpreting NNT, as readers have the tendency to over-estimate the efficacy of an intervention when results are expressed as relative rather than absolute measures.

The HR is not part of the measure of association and of effect, even if it is akin to RR. HR is found in survival analysis and represents the instantaneous event rate [30], which is the probability that an individual would experience an event at any given time point. The difference with RR is represented by the fact that if RR gives cumulative risk over a time span considering only the end of the observation period, the HR describes the instantaneous risk over a time span, incorporating time information in a more robust way.

These parameters should always be considered together with the time frame (i.e. after how long from the beginning of the treatment the outcomes are evaluated): ARR, RRR and NNT might change over time and this should be taken into account for interventions whose action might require a longer follow-up to be adequately assessed. A final remark is that every study may consider different outcomes (e.g. CV death, MACE, all-cause mortality) and different interventions. Each of those has its own ARR, RRR and NNT values to be calculated and considered in order to gain a deep understanding of the study being analysed. In the end, one should never forget that direct comparisons between different treatments are only possible with dedicated trials while comparing the results coming from separate individual studies has several limitations (comparing ARR, RRR, NNT of different studies is inappropriate) and cannot give a definite answer to clinical questions. Moreover, when implementing the results of a trial in clinical practice, one needs to go one step further, looking at ARR, RRR and NNT in the context of cost-effectiveness (cost of the intervention versus the severity of the outcome prevented). Along with these statistical indexes, the concept of "residual risk" is sometimes used. Since there is no treatment able to completely eliminate the risk of an event, this term refers to the part of the risk that still remains even after the treatment. Certainly, after all the possible statistical considerations, the most complex thing physicians have to face in their everyday clinical practice is the fact that every patient has its own "individual risk" that no method can calculate.

5. Differences and similarities between CVOTs-D and cardiovascular trials

Landmark CV trials can be effectively used as starting point for the evaluation of the magnitude of CVOTs-D results, highlighting positive and negative aspects of GLDs. Table 3 shows some of the recent and classical landmark cardiology trials, which have been chosen to encompass many pharmacological classes, different clinical indications, diverse endpoints and designs. The choice has been made in order to highlight similarities even in the context of great heterogeneity and to show how good statistical power supported the successful application of new drugs in the clinical practice.

Table 3 shows the key features of each CV trial considered. Design can vary from trials comparing two drugs head-to-head to trials assessing superiority of a drug relative to placebo. The population differs from one trial to the other, including patients with acute myocardial

Table 3
Major cardiovascular trials.

Study (ref.) year	Study drug	N. total	N. study drug	N.control	Primary endpoint	HR (95% CI)	RR (95% CI)[a]	ARR	NNT	Median follow-up
FOURIER [34] 2017	Evolocumab Vs Placebo	27564	13784	13780	Cardiovascular death, MI, stroke, hospitalization for UA, or coronary revascularization.	0.85 [0.79–0.92]	0.86 [0.80–0.92]	1.59%	63	2.2 years
TRITON-TIMI 38 [33] 2007	Prasugrel Vs Clopidogrel	13608	6813	6795	Death from cardiovascular causes, non-fatal MI, or non-fatal stroke.	0.81 [0.73–0.90]	0.82 [0.74–0.91]	2.06%	49	14.5 months (1.2 years)
PLATO [41] 2009	Ticagrelor Vs Clopidogrel	18624	9333	9291	Death from vascular causes, MI, or stroke.	0.84 [0.77–0.92]	0.85 [0.78–0.92]	1.66%	60	277 days (0.8 years)
PARADIGM-HF [31] 2014	LCZ696 Vs Enalapril	8442	4187	4212	Death from cardiovascular causes or hospitalization for HF.	0.80 [0.73–0.87]	0.82 [0.76–0.89]	4.69%	21	27 months (2.2 years)
CANTOS [42] 2017	Canakinumab Vs Placebo	10061	2170 (50 mg) 2284 (150 mg) 2263 (300 mg) 6717 (all doses)	3344	Non-fatal MI, non-fatal stroke, or cardiovascular death.	0.93 [0.80–1.07] 0.85 [0.74–0.98] 0.86 [0.75–0.99] 0.88 [0.79–0.97]	0.90 [0.79–1.03] 0.88 [0.77–1.00] 0.89 [0.78–1.01] 0.89 [0.81–0.98]	1.57% 1.99% 1.77% 1.78%	63 50 57 56	3.7 years
PEGASUS-TIMI 54 [43] 2015	Ticagrelor 90 Vs Ticagrelor 60	21162	7050 (90 mg) 7045 (60 mg) 14095 (all doses)	7067	Cardiovascular death, MI, or stroke.	0.85 [0.75–0.96] 0.84 [0.74–0.95] 0.84 [0.76–0.94]	0.86 [0.76–0.96] 0.85 [0.75–0.95] 0.85 [0.77–0.94]	1.19% 1.27% 1.23%	84 79 82	33 months (2.7 years)
IMPROVE-IT [32] 2015	Simvastatin-Ezetimibe Vs Simvastatin	18144	9067	9077	Cardiovascular death, non-fatal MI, UA requiring rehospitalization, coronary revascularization or non-fatal stroke.	0.94 [0.89–0.99]	0.94 [0.90–0.98]	1.84%	54	6 years

UA: unstable angina; MI: myocardial infarction; HF: heart failure.
[a] Calculated from the number of events and the sample size, not reported in the original publications.

infarction, chronic heart failure and patients in secondary or primary prevention. The number of participants is heterogeneous as every trial has a different statistical power, depending on the baseline risk of the study population and the expected reduction in outcomes. Similarities exist in the type of endpoints that are considered, such as all-cause mortality, CV mortality, non-fatal stroke, non-fatal myocardial infarction. End-points are usually combined because the number of events is small, therefore, only composite end-points (including similar or related event of interest) can yield significant results in adequately powered well-designed studies. Certainly, it should never be forgotten that the primary composite endpoint is made up of different components that might have a different weight in the final result and that should always be thoroughly analysed to get further information from the trial.

The main statistical parameters reported in trial analysis are shown in Table 3. RR, HR, ARR, NNT are the fundamental ones to analyse in order to derive adequate conclusions. From the general summary of Table 3, it is evident that the mean event reduction is at about 15% for the interventional group compared to the control group (the mean value of HR is 0.85, ranging from 0.80 in the PARADIGM-HF trial [31] to 0.94 in the IMPROVE-IT trial [32], for their respective primary outcome). As explained in previous paragraph, HR is a time-dependent variable and, even if RR are similar, RR is calculated at the end of the trial while HR takes into account the risk ratio at every time point, giving a better description of the event reduction. Moreover, it should be noted that even if there are some trials with a higher ARR and a lower NNT, the HR might not be so different. In PARADIGM-HF [31] and TRITON-TIMI [33] trials ARR is respectively 4.69% and 2.06% with corresponding NNT of 21 and 49. Despite this difference, HR is similar in both studies (HR 0.80 in PARADIGM-HF [31] and HR 0.81 in TRITON-TIMI [33]) expressing similar magnitude of effect in the reduction of primary outcome. HR incorporates time in a more robust way and should be the key index in the evaluation of the overall drug effect.

Median follow-ups are extremely variable. Nowadays, trials are usually shorter relative to the past, to speed up drug approval. A smaller time-window however can miss part of the treatment benefit and comparison might be more difficult. This concept is particularly important in low-moderate risk population in whom events need more time to happen. Furthermore, it should be noted that if the event curves of the two arms of a trial diverge progressively, the longer the time of observation the higher could be the difference. Non-time-dependent indices, like ARR and NNT, should be considered at different time points in the same trial to observe how risk changes over time and this is particularly critical when trying to compare these parameters. An example is the change in NNT in FOURIER [34] at 2 and at 3 years follow-up, being respectively 63 and 50, showing how risk dynamically changes over time and how indices should be critically interpreted in the time frame.

Table 1 summarizes the most important CVOTs-D that have demonstrated a clinical impact on CV outcomes, showing not only safety but even reduction in pre-specified endpoints. Empagliflozin (EMPA-REG OUTCOME [12]), liraglutide (LEADER [13]), semaglutide (SUSTAIN-6 [14]) and canagliflozin (CANVAS [15]) demonstrated a reduction of endpoints on the 3-point MACE outcome (CV death, non-fatal myocardial infarction or stroke).

The CVOTs-D for new GLDs show some differences compared to the previous trials as the introduction of new outcomes to be investigated required novel designs, in order to go beyond the simple demonstration of glycaemic control efficacy. Consequently, the new trials are structured to demonstrate non-inferiority over placebo in addition to standard care (defined as HR <1.3 to the upper boundary of 95% CI) or, if adequately powered, superiority (defined as HR <1.0 to the upper boundary of 95% CI) in reduction of pre-specified events [35]. The CVOTs-D differ from CV trials as the latter are usually designed to compare two different interventions in order to determine the best treatment option. Despite the differences, it cannot be denied that the results of the GLDs trial share similarities with those of the CV trials. The number of participants is usually smaller than that of CV trials as CVOTs-D are primarily powered to assess non-inferiority relative to placebo. Endpoints of CVOTs-D are similar to the classic CV trials, being death from cardiovascular causes, non-fatal myocardial infarction, non-fatal stroke. The endpoints have been standardized by the FDA Guidance in order to gain homogeneity and possibility of comparison between molecules. The magnitude of risk reduction is similar to the one present in cardiovascular trials. HRs of the most important CVOTs-D (Table 1) range from 0.74 in SUSTAIN-6 [14] to 0.87 in LEADER [13] trial, with a mean value of 0.83, demonstrating globally a 17% cardiovascular risk reduction by means of the novel GLDs. Likewise, the NNTs show similar values, probably underestimated due to the relatively short duration of the trial. Evaluation of NNT and ARR should be done at different time points as event curves may diverge over time. Follow-up duration is relatively short (median 3.1 years, ranging from 2.1 years in SUSTAIN-6 [14] to 3.8 years in LEADER [13]), exposing these trials to the already discussed problems related to underestimation of positive effects and masking of side-effects.

Let's consider as example one of the most recent trial in the CV field, the FOURIER [34], and one of the positive CVOTs-D of GLDs, the LEADER trial [13], to highlight common points. The FOURIER [34] trial was published in 2017. This double-blinded randomized controlled trial enrolled 27 564 patients with atherosclerosis and LDL-Cholesterol (LDL-C) >70 mg/dL to receive evolocumab or placebo. After 48 weeks of treatment, evolocumab group showed median LDL-C of 30 mg/dL (IQR 19–46), an impressive result considering that most of the patients were already receiving maximal tolerated therapy before starting the trial. Evolocumab significantly reduced the primary endpoint (composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization) compared to placebo (9.8% vs 11.3%, HR 0.85, 95% CI 0.79–0.92; $p < 0.001$) after a median follow-up of 26 months (IQR 22–30). Patients treated with evolocumab showed significant reductions in myocardial infarction (3.4% vs 4.6%, HR 0.73, 95% CI 0.65–0.82; $p < 0.001$), stroke (1.5% vs 1.9%, HR 0.79; 95% CI 0.66–0.95; $p < 0.01$), and coronary revascularization (5.5% vs 7.0%, HR 0.78, 95% CI 0.71–0.86; $p < 0.001$). As reported above, the NNT was smaller after 3 years of follow-up compared with 2 years, suggesting an effect of CV risk reduction only partially observed with relatively short follow-up. Moreover, the effect seems to be more pronounced in high-risk patients. After stratifying the patients according to the TIMI Risk Score for Secondary Prevention, it is evident that low-risk patients have an ARR of 1.2% (NNT 83) with an HR equal to 0.73 while high-risk patients have an ARR of 3.6% (NNT 28) with an HR equal to 0.80. Nevertheless, even if the median follow-up of FOURIER [34] was about 26 months, the follow-up duration of most statin trials, such as the IMPROVE-IT [32], was approximately 3 years longer. In order to take into account the shorter duration of the trial, Ference et al. conducted sub-analysis of year 0–1 and year 1–2 comparing the effect of evolocumab and previous statins [36]. On the basis of this evaluation, the number of event reduction in FOURIER [34] was comparable to the one reported in year 0–1 and year 1–2 of other lipid-lowering drugs. Consequently, this comparison suggests that a longer follow-up could highlight a mortality reduction similar to or even larger than that of previous studies, as it is reasonable to think that evolocumab needs more time to further change coronary-atheroma volume and plaque features [37].

Similarities can be found in the results of some GLDs CVOTs-D. The LEADER trial [13], published in 2016, is a randomized double-blinded placebo-controlled trial conducted on 9340 patients affected by type 2 diabetes with previous CV disease and mild degree of chronic kidney disease. The use of liraglutide resulted in a 13% reduction of the primary composite endpoint (MACE: cardiovascular death, non-fatal myocardial infarction, non-fatal stroke; HR 0.87, 95% CI 0.78–0.97, $p = 0.01$ for superiority) in a median follow-up of 3.8 years. Patients treated with liraglutide showed a reduction of 22% of cardiovascular mortality (HR 0.78, 95% CI 0.66–0.93, $p = 0.007$) and of 13% of all-cause mortality (HR 0.85, 95% CI 0.74–0.97, $p = 0.002$). The NNT in order to prevent

one MACE over 3 years of follow-up was 66. Similarly, empagliflozin in the EMPA-REG OUTCOME trial [12] showed a 14% reduction in the primary composite endpoint (HR 0.86, 95% CI 0.74–0.99, $p = 0.04$; NNT 63 over 3 years); CV death was reduced by 38% and all-cause mortality by 32%, with a relatively lower NNT for these individual endpoints. Considering these results (with the underlined limits of indirect comparisons), certainly the differences in event time-curves are interesting. In the EMPA-REG OUTCOME [12] trial there is an early separation of mortality curves (within 6–12 months) and that remained almost constant, while with liraglutide the reductions in endpoints became more evident beyond the first 12–18 months, but tended to become greater as the trial progressed. Several explanations have been proposed and the exact mechanisms by which these GLDs modify the occurrence of CV events are not completely defined. It has been suggested that empagliflozin exerted mainly a haemodynamic rather than an anti-atherogenic effect that is in line also with the reduction in hospitalizations for heart failure and the lack of any significant effect on non-fatal myocardial infarction and stroke [21]. The patterns of event reductions in the LEADER trial [13], on the other hand, might be better explained by a positive action on the atherosclerotic process, enhanced by the effect on several risk factors (namely hyperglycaemia, blood pressure and/or body weight/adiposity) [38]. As discussed before, the follow-up duration when too short might conceal the true magnitude of positive effects of treatments on CV events. Studies on statins, that yield well-demonstrated anti-atherogenic and pleiotropic effects, had a mean duration of 5 years [36]. Looking at the curves of LEADER trial [13], it can be supposed that liraglutide might progressively further increase its positive effect. The question that should be raised is the following: is the median follow-up of 2 to 4 years present in most trials enough to obtain reliable conclusions about the real effect of complex drugs such as new GLDs that have a deep impact on many modifiable risk factors all at once? We cannot be sure to observe consistently all the effects in such a short period of time, because, as shown in Kaplan-Meyer analysis, the outcome curves diverge progressively over time, suggesting that positive effects build up gradually. The “size” of the positive effect could be much larger if a larger time span is considered. Longer follow-ups are therefore needed to truly understand the impact of these drugs on long term mortality and morbidity as their cumulative effect on different risk factors sum up over time giving exponential benefit that require time to be observed.

In general, the interpretation of some statistical parameters should always be made in the light of all the points discussed above to get the correct value of the trials. For example, we cannot use NNT as the only reference index to define the benefit size as NNT changes over time and its value might describe only a small part of the positive effects. As results get more complicated to understand due to heterogeneity, the integration of all the aforementioned indices is the only way to get a more reliable and complete view of the studies, in particular taking advantage of those describing risk in a time-dependent manner (e.g. HR), gaining a broader perspective on the possible impact of drugs in everyday use. Certainly, nor NNT neither HR do not tell us everything about drug impact on the disease, on the patient itself and on the healthcare system.

Today, because of the aging of population and the increasing burden of CV and metabolic diseases with the concomitant improvement of patient care and the introduction of new drugs, health care costs are rising up. Many researchers have shown how most healthcare systems will not be able to keep up pace during the next years as the expenses will become too high [39,40]. The new GLDs and new CV/metabolic medications (e.g. PCSK9 inhibitors) are by far more expensive than the usual glucose lowering molecules and of traditional CV drugs. Nonetheless, their cost will be outweighed by the significant reduction of hypoglycaemic events and other side effects that require extensive use of medical resources (including ambulatory visits, laboratory exams, emergency department accesses). Furthermore, the positive effect on renal, cardiovascular and cerebrovascular outcomes should be taken into account when considering the cost-benefit ratio of these new generation drugs, as they can positively impact on the national healthcare costs by means of reduction of hospitalizations and cutting off the number of myocardial infarctions, strokes and need for renal replacement therapy. Obviously, all these elements go beyond initial findings clinicians read in the first publications of the trials. Furthermore, mortality should not be the only target taken into consideration, as far as morbidity can have a large negative impact on patient quality of life and society costs. Therefore, new GLDs and new CV/metabolic drugs, despite their higher cost, can represent not only an interesting tool for CV risk management by the physicians, but also a valuable future investment for the entire system.

6. Conclusions

Diabetes prevalence continues to rise worldwide and cardiovascular diseases are the main cause of death in these patients. The best management for patients with both diabetes and CV disease can only be obtained with Diabetologists and Cardiologists working strictly together. In this new clinical scenario, Cardiologists have to become confident with the new GLDs, learning how to exploit their positive impact. Likewise, Diabetologists should start considering outcomes beyond glycaemic control, aiming at long-term results. A thorough analysis of the CVOTs-D, performed considering the CV trials as reference models, represents a useful tool to increase awareness and get a deeper insight in the effect of these molecules. The magnitude of their potential beneficial impact on clinical practice clearly emerges from the analysis of CVOTs-D studies and statistical parameters. New GLDs can be powerful tools in the hands of physicians, therefore an interdisciplinary crosstalk is crucial in order to make the best use of these new weapons for the combined management of diabetes and CV risk.

Conflict of interest

Domenico Cianflone is a member of an Advisory Board for Novo Nordisk.

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