Evolving from Glycocentrism to Cardiocentrism in DM2 Treatment - Five Lessons Learned and their Clinical Implications

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Abstract

In this comprehensive short review, the designs, the results of the primary endpoint and the main clinical implications of the nine randomized-controlled trials (RCT): SAVOR-TIMI 53, EXAMINE, TECOS, ELIXA, LEADER, SUSTAIN 6, EXSCEL, EMPA-REG and CANVAS, that are evolving the way to treat type 2 Diabetes Mellitus (DM2) are summarized. This paper is devoted to review the amazing evolution from glycocentrism to cardiocentrism in the treatment of DM2, which promises for the first time in several decades to achieve a significant reduction in cardiovascular morbidity and mortality of subjects with DM2 at high cardiovascular risk, in other words, this paper reviews how and why the Cardio-Diabetology began the era of personalized treatment based on the principle of net therapeutic benefit proposed by Geoffrey Rose in the 90s of the last century.

Keywords

Diabetes Mellitus; Saxagliptin; Alogliptin; Sitagliptin; Lixisenatide; Liraglutide; Semaglutide; Exenatide; Empagliflozin; Canagliflozin

Introduction

By the end of 2017, ten years after the controversial Nissen and Wolski meta-analysis was published [1], which showed that rosiglitazone versus placebo or active comparator increased the relative risk of myocardial infarction or cardiovascular death by 43%, and influenced the publication of the 2008 FDA Guidance called “Diabetes Mellitus - Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes” [2], there are nine published randomized-controlled trials (RCTs) with 87,226 subjects included, all of them with type 2 Diabetes Mellitus (DM2) and high cardiovascular risk or established cardiovascular disease [3-11]. The results of this nine RCTs that compare the cardiovascular safety of several “Antidiabetic” molecules versus placebo on the platform of the best treatment for DM2 and risk or cardiovascular disease, allows us to affirm that the effort made in this arena of clinical research has been prolific. Thanks to the published information, at the present time we can establish that all the studied “antidiabetic” molecules are cardiovascularly safe -although, some of them showed a significant increase in hospitalization due...
to heart failure- [3]. However, the most noteworthy fact is that two receptor agonist molecules for the glucagon-like peptide type 1 (GLP-1) [8, 9] and two molecules inhibiting the sodium-glucose cotransporter type 2 (SGLT-2) [6,10] have shown a significant reduction in non-fatal events and cardiovascular death, a finding that is unexpected, but of great relevance for the reduction of global cardiovascular risk in subjects with DM2.

In this review, the designs, the results of the primary endpoint and the clinical implications of these nine RCTs that are evolving the way to treat DM2 are summarized. An evolution from glycocentrism to cardiocentrism, which promises for the first time in several decades to achieve a significant reduction in cardiovascular morbidity and mortality of subjects with DM2 and at high cardiovascular risk, using drugs originally designed for glycemic control, undoubtedly, a paradigm shift.

**FDA Guidance 2008**

Considering that in DM2, the design of phase II and III studies is aimed at demonstrating the efficacy for the reduction of glucose and HbA1c, the general safety and tolerability of the new “Antidiabetic” molecules, this with the inclusion of subjects at low cardiovascular risk, with relatively short treatment periods -3 or 6 months- and with no prospective, independent and blind adjudication of cardiovascular events, it is logical to assume that these studies are not appropriate to confirm or rule out the long-term cardiovascular safety of the studied molecules [2]. For this reason, in December 2008, the FDA published the Guidance called “Diabetes Mellitus - Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes” [2]. This document aims to suggest to the pharmaceutical industry the design, development and publication of "ad-hoc" studies to demonstrate that new molecules for the control of hyperglycemia in subjects with DM2 do not inappropriately increase the risk of a major cardiovascular event or MACE.

In order to achieve this goal, the Department of Health and Human Services of the United States FDA published in 2008 the general guidelines for the design of the so-called studies of cardiovascular outcomes (CVOT), being the most important the following three:

a) Include in long-term studies -≥2 years-, populations with DM2 and high cardiovascular risk, i.e., subjects without clinical cardiovascular disease with extra -non-glycemic- factors of cardiovascular risk, or subjects with clinical cardiovascular disease -coronary, cerebral or peripheral-.

b) Assign in a random and blind manner a therapeutic group to the study active molecule versus a group to placebo, maintaining -with an open adjustment of the “Antidiabetic” drugs of a different kind to the studied active molecule, a delta of a mean HbA1c ≤0.3% between both study groups.

c) Adjudicate in an independent and blind manner major cardiovascular events (MACE) arising during the treatment period in the active treatment group and in the placebo group.

The purpose of these guidelines is to study for appropriate periods of time the population with DM2 “enriched” with a high cardiovascular risk, to compare the cardiovascular safety -incidence of MACEs- of the active molecule versus placebo, without interference from

![Figure 1: Graph Showing Top-Down Examples of An HR with Upper Limit of the Confidence Interval (ULCI) <1 and Therefore Superior to Placebo; An HR with ULCI ≥1 and <1.3 and Therefore Non-Inferior to Placebo; and An HR with ULCI ≥1.3 and Therefore Inferior to Placebo [2]](image)
the potential effect of a significant difference in glycemic control, and adjudicate without bias the incidence of “hard” cardiovascular events such as cardiovascular death, non-fatal myocardial infarction and non-fatal cerebral infarction.

The guidelines suggested by the FDA to interpret the results of the studies with these design characteristics, can also be grouped in the following three.

a) inferiority: An active molecule will be inferior to placebo and therefore will not be authorized for commercialization if, in the “ad-hoc” study, the upper limit of the 95% confidence interval of the hazard ratio (HR) for MACEs is ≥1.3.

b) Non-inferiority: An active molecule will be non-inferior to placebo and therefore its marketing will be authorized if, in the “ad-hoc” study, the upper limit of the 95% confidence interval of the HR for MACEs is ≥1 and < 1.3.

c) Superiority: An active molecule will be superior to placebo and therefore its commercialization will be promoted if, in the “ad-hoc” study, the upper limit of 95% confidence interval of the HR for MACEs is <1.0.

The primary standard MACE or the 3-component MACE in these studies is the first incidence of cardiovascular death or non-fatal myocardial infarction and/or non-fatal cerebral infarction - cardiovascular events considered “hard” - by universal criteria for diagnosis; as secondary MACE, it is generally suggested to add hospitalization for unstable angina or coronary revascularization or heart failure to primary MACE - cardiovascular events considered “semi-hard” due to the diversity of criteria used to make such diagnostic-therapeutic decisions. Thus an “Antidiabetic” molecule may be cardiovasculaly harmful if it is inferior to placebo, cardiovascularly safe or neutral if it is non-inferior to placebo or cardiovascularly protective if it is superior to placebo.

The following is a summary of pivotal data - key inclusion criteria, primary endpoint evaluated, HR of the primary endpoint and interpretation of the results - of the nine studies published up to December 2017 under the recommendations of the 2008 FDA Guidance. After this analysis, the lessons learned in this therapeutic arena and its clinical implications will be enunciated from the author’s perspective.

**Studies with Dipeptidyl Peptidase-4 Inhibitors (IDPP-4)**

This pharmacological group was the first to publish its results under the guidelines suggested by the FDA in December 2008 [2], in chronological order, the studies and their primary results are as follows.

**Study SAVOR-TIMI 53**

Benjamin Scirica et al. published in 2013 the result of the study “Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus” [3]. This study included subjects with DM2 and HbA1c between 6.5% and 12%, men 55 years of age or older, or women 60 years of age or older with cardiovascular risk - dyslipidemia, hypertension and/or smoking - without clinical cardiovascular disease, or men or women 40 years of age or more with clinical cardiovascular disease - coronary, carotid-vertebral and/or peripheral. The primary endpoint analyzed was the first incidence of cardiovascular death or non-fatal myocardial infarction or non-fatal cerebral infarction. The study included 8,212 and 8,280 subjects in the placebo and saxagliptin -5 or 2.5 mg orally per day adjusted for glomerular filtration rate (GFR)- groups, respectively. In a mean follow-up period of 24 months, the incidence of primary MACE was 7.2% (609 MACEs) versus 7.3% (613 MACEs) in the placebo and saxagliptin groups, respectively; the HR for saxagliptin was 1.0 with confidence intervals ranging from 0.89 to 1.12 and a p-value of <0.001 for non-inferiority and 0.99 for superiority. This way, saxagliptin compared to placebo is a non-inferior, neutral or cardiovascularly safe molecule in subjects with DM2 and high cardiovascular risk or cardiovascular disease [3].

**Study EXAMINE**

William White et al. published in 2013 the result of the study “Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care” [4]. This study included subjects with DM2 and HbA1c between 6.5% and 11% - on non-insulin therapy - or between 7% and 11% - on insulin therapy - with a history of an acute coronary syndrome - myocardial infarction or unstable angina - within 15 and 90 days of study enrollment. The primary endpoint analyzed was the first incidence of cardiovascular death or non-fatal myocardial infarction or non-fatal cerebral infarction. The study included 2,679 and 2,701 subjects in the placebo and alogliptin groups -25, 12.5 or 6.25 mg orally per day adjusted for GFR, respectively. In a mean follow-up period of 18 months, the incidence of primary MACE was 11.8% (316 MACEs) versus 11.3% (305 MACEs) in the placebo and alogliptin groups, respectively; the HR for alogliptin was 0.96 with confidence intervals ranging from 0.76 and 1.16.
and a p-value of <0.001 for non-inferiority and 0.32 for superiority. Thus, alogliptin compared to placebo, just like saxagliptin, is a non-inferior, neutral or cardiovascularly safe molecule in subjects with DM2 and cardiovascular disease [4].

Study TECOS

Jennifer Green et al. published in 2015 the result of the study “Trial Evaluating Cardiovascular Outcomes with Sitagliptin” [5]. This pioneering study for its design, prior to the publication of the FDA Guideline 2008, included subjects with DM2 and HbA1c between 6.5% and 8%, men or women aged 50 years or older, with clinical cardiovascular disease -coronary, carotid-vertebral and/ or peripheral- and renal function with a calculated GFR of ≥30 ml/min/1.73m2. The primary endpoint analyzed was the first incidence of cardiovascular death or non-fatal myocardial infarction or non-fatal cerebral infarction or hospitalization due to unstable angina (MACE extended).

The study included 7,339 and 7,332 subjects in the placebo and sitagliptin groups -100 or 50 mg orally per day adjusted for GFR-, respectively. In a mean follow-up period of 36 months, the incidence of primary MACE was 11.6% (851 MACEs) versus 11.4% (839 MACEs) in the placebo and sitagliptin groups, respectively; the HR for sitagliptin was 0.98 with confidence intervals ranging from 0.89 to 1.08 and a p-value of <0.001 for non-inferiority and 0.65 for superiority. With these results, sitagliptin compared to placebo, as well as saxagliptin and alogliptin, is a non-inferior, neutral or cardiovascularly safe molecule in subjects with DM2 and cardiovascular disease [5].

In summary, subject to knowing the results of the cardiovascular safety studies with linagliptin versus glimepiride [12] and versus placebo [13], so far it can be concluded that saxagliptin, alogliptin and sitagliptin are non-inferior or cardiovascularly safe molecules compared to placebo in subjects with cardiovascular risk or clinical cardiovascular disease [3-5].

In this section, it is important to note that, in pre-specified analyzes, in the study SAVOR-TIMI 53 [14], saxagliptin compared to placebo showed a significant increase in the incidence of hospitalization due to heart failure -2.8% versus 3.5% - with a HR for saxagliptin of 1.27% with confidence intervals ranging from 1.07 to 1.51 and a p-value of 0.007 -number needed to harm (NNH) 142/24 months-; in the study EXAMINE [15], alogliptin compared to placebo showed a non-significant increase in the incidence of hospitalization due to heart failure -2.9% versus 3.1% - with a HR for alogliptin of 1.07 with confidence intervals ranging from 0.79 to 1.46 and a non-significant p-value; finally, in the study TECOS [5], sitagliptin compared to placebo showed no increase in the incidence of hospitalization due to heart failure -3.1% versus 3.1% - with a HR for sitagliptin of 1.0 with confidence intervals ranging from 0.83 to 1.20 and a non-significant p-value. In the sub-analyses of saxagliptin and alogliptin, the history of heart failure, the elevation of natriuretic peptides -N-terminal pro-brain natriuretic peptide (NT-proBNP) > 300 pg/ml- and the decrease in GFR - <60 ml/min/1.73m2- were predictive variables.
of cardiovascular death and hospitalization due to heart failure [14, 15].

**Glucagon-Like Peptide-1 Receptor Agonists (arGLP-1)**

**Study ELIXA**

Marc Pfeffer et al. published in 2015 the result of the study “Evaluation of Lixisenatide in Acute Coronary Syndrome” [7]. This study included subjects with DM2 and HbA1c between 5.5% and 11% with a history of an acute coronary syndrome -myocardial infarction or unstable angina- within 180 days of study enrollment and renal function with a calculated GFR of ≥30 ml/min/1.73m2. The primary endpoint analyzed was the first incidence of cardiovascular death or non-fatal myocardial infarction or non-fatal cerebral infarction or hospitalization due to unstable angina (MACE extended). The study included 3,034 and 3,034 subjects in the placebo and lixisenatide groups -20 mcg S.C per day-, respectively. In a mean follow-up period of 25 months, the incidence of primary MACE was 13.2% (399 MACEs) versus 13.4% (406 MACEs) in the placebo and lixisenatide groups, respectively; the HR for lixisenatide was 1.02 with confidence intervals ranging from 0.89 to 1.17 and a p-value of <0.001 for non-inferiority and 0.81 for superiority. Hence, lixisenatide compared to placebo is a non-inferior, neutral or cardiovascularly safe molecule in subjects with DM2 and cardiovascular disease [7].

**Study LEADER**

Steven Marso et al. published in 2016 the result of the study “Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results” [8]. This study included subjects with DM2 and HbA1c ≥7%, men or women aged 60 years or older, with cardiovascular risk -proteinuria, hypertension with hypertrophy and/or left ventricular dysfunction or asymptomatic ankle/arm index <0.9 -, without clinical cardiovascular disease or renal failure or heart failure, or either men or women aged 50 years or older, with clinical cardiovascular disease -coronary, carotid- vertebral or peripheral- or renal failure -modification of diet in renal disease (MDRD) class II-V- or heart failure - New York Heart Association (NYHA) class II-III-. The primary endpoint analyzed was the first incidence of cardiovascular death or non-fatal myocardial infarction or non-fatal cerebral infarction. The study included 4,672 and 4,668 subjects in the placebo and liraglutide groups -1.8 mg S.C per day-, respectively. In a mean follow-up period of 46 months, the incidence of primary MACE was 14.9% (694 MACEs) versus 13.0% (608 MACEs) in the placebo and liraglutide groups, respectively; the HR for liraglutide was 0.87 with confidence intervals ranging from 0.78 to 0.97 and a p-value of <0.001 for non-inferiority and 0.01 for superiority. The relative and absolute risk reduction for the primary endpoint was 13% and 1.9%, respectively, with a number needed to treat (NNT) of 52 in 3.8 years.

In the pre-specified hierarchical analysis of the individual components of the primary endpoint, liraglutide compared to placebo significantly reduced the isolated incidence of cardiovascular death -6.0% versus 4.7% - with an HR for liraglutide of 0.78 with confidence intervals ranging from 0.66 and 0.93 and a p-value of 0.007; the relative and absolute risk reduction for cardiovascular death was 22% and 1.7%, respectively, with an NNT of 77 in 3.8 years. Liraglutide compared to placebo reduced in a non-significant manner the isolated incidence of non-fatal myocardial infarction -HR 0.88: 0.75 to 1.03- and of non-fatal cerebral infarction -HR 0.89: 0.72 to 1.11-. Liraglutide compared to placebo significantly reduced the isolated incidence of total death -9.6% versus 8.2% - with an HR for liraglutide of 0.85 with confidence intervals ranging from 0.74 and 0.97 and a p-value of 0.02; the relative and absolute risk reduction for total death was 15% and 1.4%, respectively, with an NNT of 71 in 3.8 years.

With these results, for the first time among the GLP-1 receptor agonists, liraglutide proved to be a superior or cardiovascularly protective molecule compared to placebo in subjects with DM2 and high cardiovascular risk or with cardiovascular disease, including heart failure and renal failure. In LEADER, the type of events prevented and the chronology of the appearance of the therapeutic benefit of liraglutide from the second year of treatment suggest an anti-atherosclerotic effect. These clinical observations indirectly correlate with mechanistic hypotheses that suggest cardio- and endothelium-protective effects, which will be analyzed later.

**Study SUSTAIN 6**

Steven Marso et al. published in 2016 the result of the study “Trial to Evaluate Cardiovascular and other Cardiovascular Outcomes with Semaglutide in Diabetes Mellitus Type 2” [9]. This study, similarly to the study LEADER [8], included subjects with DM2 and HbA1c ≥7%, men or women aged 60 years or older, with cardiovascular risk -proteinuria, hypertension with hypertrophy and/or left ventricular dysfunction or asymptomatic ankle/arm function with a calculated GFR of ≥30 ml/min/1.73m2.
index <0.9 -, without clinical cardiovascular disease or kidney failure or heart failure, or either men or women aged 50 or older, with clinical cardiovascular disease -coronary, carotid-vertebral or peripheral- or renal failure -MDRD class II- V- or heart failure -NYHA class II-III-. With a pre-approval phase design -upper limit of the HR confidence interval <1.8-, the primary endpoint analyzed was the first incidence of cardiovascular death or non-fatal myocardial infarction or non-fatal cerebral infarction. The study included 1,648 and 1,649 subjects in the placebo and semaglutide groups -1.0 mg or 0.5 mg S.C per week, respectively. In a mean follow-up period of 25 months, the incidence of primary MACE was 8.9% (146 MACEs) versus 6.6% (108 MACEs) in the placebo and semaglutide groups, respectively; the HR for semaglutide was 0.74 with confidence intervals ranging from 0.58 and 0.95 and a p-value of <0.001 for non-inferiority and 0.02 for superiority - a non-pre-specified analysis -; the relative and absolute risk reduction for the primary endpoint was 26% and 2.3%, respectively, with an NNT of 23 in 2.1 years.

In the pre-specified hierarchical analysis of the components of the primary endpoint, semaglutide compared to placebo did not significantly reduce the isolated incidence of cardiovascular death -HR 0.98: 0.65 to 1.48; semaglutide compared to placebo significantly reduced the isolated incidence of non-fatal cerebral infarction -2.7% versus 1.6% with an HR for semaglutide of 0.61 with confidence intervals ranging from 0.38 and 0.99 and a p-value of 0.04; semaglutide compared to placebo reduced in a non-significant manner the isolated incidence of non-fatal myocardial infarction -HR 0.74: 0.51 to 1.08.

With this result and with a non-inferiority pre-approval phase design, semaglutide compared to placebo proved to be a not inferior or cardiovascularily neutral molecule compared to placebo in subjects with high cardiovascular risk or cardiovascular disease, including heart failure and renal failure. The superiority analysis for semaglutide over placebo, although not pre-specified in this study, is highly probable and will have to be confirmed in a study that pre-specifies as <1.3 the upper limit of the HR confidence interval for the primary endpoint.

**Study EXSCEL**

Rury Holman et al. published in 2017 the result of the study “Exenatide Study of Cardiovascular Event lowering” [11]. This “pragmatic” design study included subjects 18 years of age or older, with DM2 and HbA1c between 6.5% and 10%, with any level of cardiovascular risk or clinical cardiovascular disease and a GFR ≥30 ml/min/1.73m². The primary endpoint analyzed was the first incidence of cardiovascular death or non-fatal myocardial infarction or non-fatal cerebral infarction. The study included 7,396 and 7,356 subjects in the placebo and exenatide -2 mg S.C per week- groups, respectively. In a mean follow-up period of 38 months, the incidence of primary MACE was 12.2% (905 MACEs) versus 11.4% (839 MACEs) in the placebo and exenatide groups, respectively; the HR for exenatide was 0.91 with confidence intervals ranging from 0.83 to 1.00.

**Figure 3:** Graph Showing HR and ULCI for the Primary Endpoint in Studies ELIXA with Lixisenatide, LEADER with Liraglutide, SUSTAIN 6 with Semaglutide and EXSCEL with Exenatide. For the Four Molecules, the HR is at 1 or to the Left of the Neutrality Line, However, Only for Liraglutide and Semaglutide the ULCI is <1, which means Superiority Versus Placebo or Cardioprotection; Lixisenatide and Exenatide Maintain a ULCI ≥1 and <1.3, which means that they are Non-Inferior Compared to Placebo and Therefore Cardiovascularily Safe [7-9, 11]
and 1.0 and a p-value of <0.001 for non-inferiority and 0.06 for superiority. With this result, exenatide compared to placebo, similarly to lixisenatide, is a non-inferior, neutral or cardiovascularly safe molecule in subjects with cardiovascular risk or cardiovascular disease [11]. Thus, among the GLP-1 receptor agonists, subject to knowing the results of cardiovascular safety studies with dulaglutide [16] and albiglutide [17], so far it can be concluded that lixisenatide and exenatide are non-inferior or cardiovascularly safe molecules compared to placebo. Liraglutide is a superior or cardiovascularly protective molecule compared to placebo, which significantly reduces the incidence of the combined primary endpoint of cardiovascular death, non-fatal myocardial infarction and/or non-fatal cerebral infarction, as well as the isolated incidence of cardiovascular death and total death. Semaglutide in the study SUSTAIN 6 - with a pre-approval phase design with a pre-specified margin <1.8 for the upper limit of the HR confidence interval - surprisingly reduced in a significant manner the incidence of the combined primary endpoint of cardiovascular death, non-fatal myocardial infarction and/or non-fatal cerebral infarction, thereby confirming its non-inferiority and opening the opportunity to confirm its superiority versus placebo.

Regarding the incidence of hospitalization for heart failure, no member of this therapeutic class increases or decreases this MACE - lixisenatide HR 0.96: 0.75 to 1.23, liraglutide HR 0.87: 0.73 to 1.05 and exenatide HR 0.94: 0.78 to 1.13. [7, 8, 11].

Sodium-Glucose Co-Transporter 2 Inhibitors (iSGLT-2)

Study EMPA-REG

Bernard Zinman et al. published in 2015 the result of the study “Empagliflozin Removal of Access of Glucose Outcome Trial” [6]. This study included subjects with DM2 and HbA1c between 7% and 9% with clinical cardiovascular disease -coronary, carotid-vertebral or peripheral-. The primary endpoint analyzed was the first incidence of cardiovascular death or non-fatal myocardial infarction -symptomatic myocardial infarctions were excluded- or non-fatal cerebral infarction. The study included 2,333 and 4,687 subjects in the placebo and empagliflozin groups - 2,345 and 2,342 in empagliflozin 10 and 25 mg orally per day, respectively. In a mean follow-up period of 37 months, the incidence of primary MACE was 12.1% (282 MACEs) versus 10.5% (490 MACEs) in the placebo and empagliflozin groups -both doses-, respectively; the HR for empagliflozin was 0.86 with confidence intervals ranging from 0.74 to 0.99 and a p-value of <0.001 for non-inferiority and 0.04 for superiority; the relative and absolute risk reduction for the primary endpoint was 14% and 1.6%, respectively, with an NNT of 62 in 3.1 years.

In the pre-specified hierarchical analysis of the components of the primary endpoint, empagliflozin compared to placebo significantly reduced the isolated incidence of cardiovascular death -5.9% versus 3.7% with an HR of 0.62 for empagliflozin with confidence intervals ranging from 0.49 to 0.67 and a p-value of <0.001; the relative and absolute risk reduction for cardiovascular death was 38% and 2.2%, respectively, with an NNT of 45 in 3.1 years. Empagliflozin compared to placebo reduced in a non-significant manner the isolated incidence of non-fatal myocardial infarction -HR 0.88: 0.70 to 1.09- and showed a non-significant increase in the isolated incidence of non-fatal cerebral infarction -HR 1.24: 0.92 to 1.67-. Empagliflozin compared to placebo significantly reduced the isolated incidence of total death -8.3% versus 5.7%- with an HR for empagliflozin of 0.68 with confidence intervals ranging from 0.57 to 0.82 and a p-value of <0.001; the relative and absolute risk reduction of total death was 32% and 2.6%, respectively, with an NNT of 38 in 3.1 years.

In 2015, for the first time among all the therapeutic classes analyzed, empagliflozin compared to placebo proved to be a superior or cardiovascularly protective inhibitory molecule of the SGLT-2 in subjects with DM2 and cardiovascular disease. In contrast to what was observed for the GLP-1 receptor agonists, the type of prevented events, especially the highly significant reduction of hospitalization due to heart failure -HR 0.65: 0.50-0.85 with p 0.002-, and the chronology of the therapeutic benefit appearance in a period as short as the first six months of treatment, suggest a favorable “metabolodiuretic” effect, a term coined by Verma et al. [18]. This pattern of clinical benefit indirectly correlates with mechanistic hypotheses that suggest predominantly cardio-renal effects, which will be analyzed later.

Study CANVAS

Bruce Neal et al. published in 2017 the result of the study “Canagliflozin Cardio-Vascular Assessment Study” [10]. This study included subjects with DM2 and HbA1c between 7% and 10.5%, men or women aged...
50 years or older with cardiovascular risk - DM2 >10 years, systolic blood pressure >140 mmHg on treatment, smoking, micro-macroalbuminuria and/or HDL-C <38.7 mg/dl, or men or women aged 30 years or older with clinical cardiovascular disease -coronary, carotid-vertebral or peripheral, both groups with GFR ≥30 ml/min/1.73m². The primary endpoint analyzed was the first incidence of cardiovascular death or non-fatal myocardial infarction or non-fatal cerebral infarction. The study included 4,347 and 5,795 subjects in the placebo and canagliflozin groups -300 or 100 mg orally per day. In a mean follow-up period of 46 months, the incidence of primary MACE was 31.5 versus 26.9 MACEs/1000 subjects-treatment year in the placebo and canagliflozin both doses- groups, respectively; the HR for canagliflozin was 0.86 with confidence intervals ranging from 0.75 to 0.97 and a p-value of <0.001 for non-inferiority and 0.02 for superiority; the relative and absolute risk reduction for the primary endpoint was 14% and 4.6% per 1,000 subjects-treatment year, respectively, with an NNT of 22 per 1000 subjects-treatment year.

In the pre-specified hierarchical analysis of the components of the primary endpoint, canagliflozin compared to placebo did not significantly reduce the isolated incidence of cardiovascular death -HR 0.87: 0.72 to 1.06, nor the isolated incidence of non-fatal myocardial infarction -HR 0.85: 0.69 to 1.05 or non-fatal cerebral infarction -HR 0.90: 0.71 to 1.15. Canagliflozin compared to placebo did not significantly reduce the isolated incidence of total death -HR 0.87: 0.74 to 1.01.

Canagliflozin, similarly to empagliflozin, proved to be a superior or cardiovascularly protective SGLT-2 inhibitory molecule compared to placebo in subjects with DM2 and cardiovascular disease. However, in contrast to empagliflozin, canagliflozin has no significant effect beyond the reduction of the combined primary endpoint of cardiovascular death, non-fatal myocardial infarction and/or non-fatal cerebral infarction. Additionally, the referred benefit is diluted by a significant increase in the incidence of acral amputations of toes with 6.3 versus 3.4 amputations/1000 subjects-treatment year -HR 1.97: 1.41 to 2.75. Canagliflozin shares with empagliflozin the significant reduction of hospitalization due to heart failure with -HR 0.67: 0.52-0.87-, with an early benefit pattern reaffirming a metabolodiuretic effect of the SGLT-2 inhibitors.

Hitherto, subject to knowing the results with dapagliflozin [19] and ertugliflozin [20], it can be concluded that both SGLT-2 inhibitors are superior or cardiovascularly protective molecules compared to placebo, which significantly reduce the incidence of the combined primary endpoint of cardiovascular death, non-fatal myocardial infarction and/or non-fatal cerebral infarction, a statistically stronger benefit for empagliflozin given the significant reduction in cardiovascular death and total death as isolated endpoints; both molecules significantly reduce hospitalization due to heart failure, and as mentioned before, canagliflozin increased the risk of acral amputation of toes with an NNH of 5/1,000/5 treatment years.

Lessons Learned and Clinical Implications

Lesson 1: The Control of a Biochemical Marker
such as HbA1c does not Guarantee the Reduction of Cardiovascular Morbidity and Mortality

The glycocentric concept -control of DM2 based on the reduction of glycemia/HbA1c-, although it has validated the significant reduction of acute complications of hyperglycemia and microvascular complications of DM2 -retinopathy, nephropathy and neuropathy- [21], it has not corroborated the significant reduction in the incidence of cardiovascular disease in subjects with DM2 [22-24], furthermore, evidence persists that the reduction of glycemia/HbA1c through certain mechanisms or molecules [1] or at HbA1c control levels of <6.5% could be cardiovascularly deleterious [22].

Thus, although control of glycemia/HbA1c in subjects with DM2 should be a universal tactic [25], the strategy to carry it out should be individualized, especially now that we have molecules with different profiles of net therapeutic benefit, some of which, like liraglutide or empagliflozin, facilitate reaching our cardiocentric goal in DM2, that is, reducing the incidence of fatal and non-fatal cardiovascular events and thereby increasing the quality survival for this population.

Lesson 2: The Class Effect between “Antidiabetic” Molecules does not exist

The reviewed evidence shows that the cardiovascular impact is different between molecules of the same therapeutic class. With the understanding that only “face-to-face” studies can confirm the equivalence, superiority or inferiority of two molecules of the same or different therapeutic class, so far, the reviewed evidence shows different profiles of cardiovascular safety between the molecules and the analyzed therapeutic classes. The three DPP-4 inhibitors studied are as cardiovascularly safe as placebo, which is why they are therapeutic options complying 100% the requested by the FDA [2, 3-5], making the statement that saxagliptin and to a lesser degree alogliptin would be relatively contraindicated in subjects with DM2 and a history of clinical heart failure, GFR <60mL/min/1.73m² and/or NT-proBNP >300pg/ml [14, 15]. Among GLP-1 receptor agonists approved for clinical use, lixisenatide and exenatide, as well as DPP-4 inhibitors, are as cardiovascularly safe as placebo and do not increase the risk of hospitalization due to heart failure [7, 11]. Liraglutide is a cardiovascularly superior molecule compared to placebo, meaning that it significantly reduces, compared to the “standard of care”, the incidence of the first event of cardiovascular death or non-fatal myocardial infarction and/or non-fatal cerebral infarction, a benefit dominated by the significant reduction in cardiovascular death -NNT 77/3.8 years-, with a significant reduction in total death -NNT 71/3.8 years [8]. Liraglutide, just as its group partners, does not reduce or increase the incidence of hospitalization due to heart failure. Regarding the SGLT-2 inhibitors studied, both are cardiovascularly superior molecules compared to placebo, they significantly reduce, compared to the “standard of care”, the incidence of the first event of cardiovascular death or non-fatal myocardial infarction and/or non-fatal cerebral infarction [6, 10]. However, the net clinical benefit is stronger for empagliflozin since, in contrast to canagliflozin, the former showed a significant reduction in the isolated incidence of cardiovascular death -NNT 45/3.1 years- and total death -NNT 38/3.1 years; both molecules significantly reduce...
the incidence of hospitalization due to heart failure [6, 10], and in an unexplained but clinically significant manner, canagliflozin increases the incidence of acral amputations of the lower limbs [10].

Lesson 3: Until Today it can be Proposed that Liraglutide is a Cardioprotective Molecule that Reduces Cardiovascular Morbidity and Mortality with a Chronological Profile and by Mechanisms Suggesting an Anti-Atherosclerotic Effect

This proposal is based on the chronology of the clinical benefit and on the mechanisms proposed to explain it. In the study LEADER [8], the incidence curves of the primary endpoint between liraglutide and placebo began to separate significantly after the second year of treatment. This chronological profile of clinical benefit is similar to that published in 2005 for medium-intensity statins versus placebo by the “Cholesterol Treatment Trialist’s Collaboration Group” or CTT-2005 [26], and more recently for evolocumab versus placebo by the “Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk” or study FOURIER [27]. The first reported a significant reduction of 10% for the primary endpoint in the first year of treatment and 25% starting from the second year of treatment; the second published a significant reduction of 16% for the primary endpoint in the first year of treatment and 25% starting from the second year of treatment. This chronological profile of the therapeutic benefit has been considered “classic” for anti-atherosclerotic therapies and is explained by the medium and long-term latency in the installation of anti-atherosclerotic processes, a phenomenon demonstrated in the most recent trials with intracoronary ultrasound with statins [28] and evolocumab [29].

Based on evidence from basic, preclinical and clinical research, and with the purpose of giving a mechanistic explanation for the result of the study LEADER, several researchers have proposed mechanisms mediated by GLP-1 or by its truncated peptides (GLP-1 [9-36], GLP-1 [9-37] and GLP-1 [29-36]) through the GLP-1 receptor itself, from “alternate” receptors for GLP-1 or directly in intracellular enzymatic cascades, e.g., AMP-kinase. This topic has recently been reviewed extensively by Nauck, Drucker et al. [30]. From this extensive review, see below, we summarize those non-metabolic mechanisms with a potential effect of endothelium- and cardio-protection.

a) Endothelium: The presence of GLP-1 receptors has been demonstrated in endothelial cells. Through the agonism of the GLP-1 receptor, of “alternate” GLP-1 receptors or by intracellular effect of truncated GLP-1 peptides, it has been reported an increase in progenitor endothelial cells; an increase in nitric oxide synthase and nitric oxide synthesis with decreased endothelin-1; a reduction of the production of O2 free radicals in endothelial cells and in monocytes with decrease of...
inflammatory cytokines and increase of adiponectin; finally, in megakaryocytes an increase in cAMP has been observed. All these direct or indirect actions of GLP-1 agonism could explain the vasodilation, the angiogenesis, the anti-inflammatory effect, the platelet anti-adhesion and the reduction of carotid intima-media thickness reported by several researchers in experimental models [30].

b) Heart: The presence of GLP-1 receptors has been demonstrated in atria (including the sinoatrial node) and in ventricles. The agonism of these receptors determines an increase in chronotropism and inotropism; however, the biochemical -NT-proBNP- and clinical outcomes in subjects with heart failure have not been favorable with the use of such strategy [30]. In models of myocardial ischemia/reperfusion, the GLP-1 receptor agonism has been shown to reduce the necrosis area and improve the contractility of the ischemic area at risk, a phenomenon explained through the reduction of the production of O$_2$

Figure 7: Graph Showing the Latency Time for the Appearance of the Therapeutic Benefit in Study EMPA-REG with Empagliflozin. In this Study, The Incidence Curves for the Primary Endpoint began to Separate in Favor of Empagliflozin in the First Semester of Treatment, Reaching a Significant Reduction of 14% and 1.6% in Relative and Absolute Risks, Respectively, at 3.1 Years of Treatment, which is Equivalent to An NNT of 62/3.1 Treatment Years [6]

Figure 8: The Effects that SGLT-2 Inhibitors Exert beyond their “Classic” Glucosuric Effect are Summarized. At the Level of the Kidney by Stimulation of the Macula Densa, the Tubuloglomerular Feedback is Activated with Afferent Vasoconstriction and Reduction of the Intraglomerular Pressure; in Addition, Reduction of Body Sodium Deposits in the Skin and the Muscle has been Documented. At the Renal Level, the NHE-3 Inhibition Favors the Excretion of Bicarbonate and Natriuresis; at the Cardiac Level, the NHE-3 Inhibition Favors the Reduction of Calcium Entry into the Cytoplasm with an Increase of Calcium Entry into the Mitochondria, which has a Potential Cardioprotective Effect [18, 31, 32]
free radicals and the increase in AMP-kinase activity with activation of the GLUT-4 and CD-36 transporters, increase of intracellular glucose and free fatty acid entry into the cardiomyocyte with increased ATP production [30].

**Lesson 4: In Contrast to Liraglutide, Current Evidence Suggests that Empagliflozin is a Cardioprotective Molecule that Reduces Cardiovascular Morbidity and Mortality with a Chronological Profile and by Mechanisms that Involve a “Metabolodiuretic” Effect [18]**

This suggestion is based on the chronology of the clinical benefit and on the mechanisms proposed to explain it up to date. Especially, in the study EMPA-REG [6] the incidence curves for the primary endpoint between empagliflozin and placebo began to separate significantly after the sixth month of treatment, this chronological profile suggests a metabolic-hemodynamic mechanism related to the generation of high energy substrates, changes in intravascular volume and/or changes in arterial vascular function.

Similarly, to liraglutide, with the scientific intention to give a mechanistic explanation for the results of studies with SGLT-2 inhibitors, recently -based on basic, preclinical and clinical evidence- multiple mechanisms mediated by the inhibition of SGLT and other associated transporters, especially the sodium–hydrogen exchanger 3 (NHE-3) have been proposed. Several authors [18, 31, 32] have proposed and recently compiled the mechanisms with most evidence to explain the clinical benefit of the SGLT-2 inhibitors, among them, the most outstanding ones are summarized below.

a) Glucosuric effect: The first hypotheses to explain the benefit of SGLT-2 inhibitors suggested that glycosuria induced by the effect of these drugs on the proximal renal tubule causes osmotic diuresis with intravascular volume depletion, ventricular preload reduction and myocardial O2 consumption reduction, the latter also favored by the reduction of arterial stiffness and ventricular afterload. Furthermore, it was postulated that glycosuria and the insulin/glucagon imbalance associated with the inhibition of SGLT-2 favors the hepatic production of ketones, especially β-hydroxy butyrate, a high-efficiency substrate for the production of ATP by the cardiomyocyte [18, 31, 32].

b) Tubuloglomerular feedback. More recently, it has been proposed that the proximal blockade of sodium and water reabsorption determines an increase in osmolality and hydrostatic pressure at the distal tubule level, these osmotic and hemodynamic changes activate in the macula densa the so-called tubuloglomerular feedback with vasoconstriction of the afferent arteriole and reduction of intra-glomerular pressure [18]; this tubuloglomerular hemodynamic mechanism accounts for 30-40% of the reduction in albuminuria observed with the pharmacological inhibition of SGLT-2 [32].

c) Body sodium depletion. The skin and the muscle are important deposits of sodium, and the concentration of sodium in these tissues is directly related to the increase in blood pressure and the decrease in ventricular function [32]. Recently, with the use of labeled sodium and nuclear magnetic resonance (NMR), it has been documented that the inhibition of SGLT-2 with dapagliflozin determines a significant reduction in the concentration of sodium in skin deposits, a fact that could contribute to the reduction of blood pressure and improvement of ventricular function [32].

d) Inhibition of the NHE-3. At the renal level, blockade of SGLT-2 is associated to a parallel blockade of NHE-3, which determines an increase in renal excretion of bicarbonate and a decrease in sodium reabsorption. At the cardiomyocyte level, although the absence of SGLT-2 is demonstrated, the inhibition of NHE-3 in the cardiomyocyte favors the reduction of sodium and calcium entry into the cytosol with increased calcium entry into the mitochondria; the increase of mitochondrial calcium activates the generation of ATP and antioxidant enzymatic cascades [31].

**Lesson 5: Cardio-Diabetology Began the Era of Personalized Treatment Based on the Principle of Net Therapeutic Benefit Proposed by Geoffrey Rose in the 90s of the Last Century [33]**

This principle, currently applied to the treatment with statins, is based on the premise that a drug or a biological product is useful only if it complies with the equation: benefit > risk and saving > expense. Thus, according to this principle, an individual is at high risk or a candidate for treatment not because of the level of the risk “per se” but because of the existence of a therapy that provides a net therapeutic benefit with a favorable ratio.

In the context of the current subject and focusing on the cardiovascular benefit, it is evident that beyond the cardiovascular safety shown by all the analyzed molecules, liraglutide and empagliflozin fulfill the numerator of the equation –benefit > risk-; to demonstrate the second part of the equation will require specific cost-effectiveness
studies for each country. Liraglutide and empagliflozin in the population with DM2 and high cardiovascular risk -80% with established cardiovascular disease- are effective in reducing the combined factors of cardiovascular death, non-fatal myocardial infarction and non-fatal cerebral infarction; the MACE NNT compound for liraglutide is 52 in 3.8 years and for the empagliflozin is 62 in 3.1 years, both with a favorable impact on cardiovascular death as an isolated variable (NNT 77/3.8 years and 41/3.1 years, respectively). Due to these numbers, both drugs have been suggested as the drugs of “choice” in the population with DM2 and established cardiovascular disease [34]. In addition, empagliflozin has been approved by the FDA since December 2016 for the indication of cardiovascular mortality reduction in subjects with DM2 and established cardiovascular disease [35], in the same way, liraglutide has been approved by the same agency since August 2017 for the indication of reduction of cardiovascular death, non-fatal myocardial infarction and/or non-fatal cerebral infarction in subjects with DM2 and established cardiovascular disease [36].

However, in addition to the saving/expense balance still to be defined for liraglutide and empagliflozin, the question - not confronted by the Guidelines - of greater clinical relevance is: what should be the drug of choice, liraglutide or empagliflozin?

Considering that a “face-to-face” study with both molecules, including their combination, looks desirable but is unlikely, in the opinion of the author, within the framework of the cardiovascular continuum of Dzau and Braunwald and considering the chronology of the therapeutic benefit and the mechanisms already reported to explain it, liraglutide seems an appropriate molecule for subjects with DM2 and at high atherothrombotic risk, e.g., recent acute coronary syndrome -<6 months-, clinically unstable coronary disease or clinically stable coronary disease with positive markers of myocardial ischemia; on the other side empagliflozin is proposed as an appropriate molecule in subjects with DM2 and at high risk of- or with heart failure e.g., history of heart failure, ventricular ejection fraction <40%, NT-proBNP >300 pg/ml and/or GFR <45-60ml/min/1.73m² (the latter, for now, would be an “off-label” indication).

While both clinical profiles often overlap, the author’s proposal intends to be an orientation for the clinician who does not find in the Guidelines a specific orientation for the selection between the two therapeutic classes and the 2 molecules studied and approved for cardiovascular secondary prevention in patients with DM2 [35, 36].

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