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Assessing the Cardiovascular Safety of Novel Diabetes and Obesity Medications – Implications for Early Phase Development

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Key Focus Points

- The FDA requires that new glucose-lowering and anti-obesity agents demonstrate cardiovascular safety.
- While many approved diabetes drugs and new obesity drugs have been shown to improve cardiometabolic risk factors, they have not been rigorously characterized in their cardiovascular profiles.
- The cardiovascular effects of novel compounds can be rigorously assessed in early phase development using advanced imaging and circulating and/or functional methodologies to inform development decisions based on early signs of cardiovascular risk or benefit.
- Robust characterization of the cardiovascular effects of a novel therapy during early development is a safe and cost-effective way to identify potential cardiovascular risk prior to initiating large, expensive phase 3 or 4 cardiovascular outcome trials.

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Introduction

Excess weight and obesity are considered key drivers of the type 2 diabetes mellitus (T2DM), non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), and cardiovascular disease (CVD) pandemics. Collectively, more than two-thirds of adults in the United States are overweight or obese. Pharmacotherapy, in addition to calorie restriction and increased physical activity, is indicated for patients with a body mass index (BMI) ≥30 or ≥27 kg/m^2 in the presence of other risk factors. There are currently five long-term pharmacological treatments for obesity (orlistat, lorcaserin, phentermine-topiramate, bupropion-naltrexone, liraglutide) approved by the United States Food and Drug Administration (FDA); of these, four were approved after 2010. The adoption of anti-obesity drugs in a clinical setting has been slow, particularly compared to the adoption of newer glucose-lowering agents such as dipeptidyl peptidase (DPP)-4 inhibitors, glucagon-like peptide (GLP)-1 receptor agonists, and sodium-glucose cotransporter (SGLT)-2 inhibitors. For example, between 2012 and 2015, SGLT-2 inhibitors were adopted at an exponential rate, compared to a linear adoption curve for novel anti-obesity pharmacotherapies.

There are clear regulatory distinctions between novel glucose-lowering and anti-obesity drugs; however, there is increasingly overlap between the glucose-lowering and weight-reduction functions of novel pharmacotherapies. For example, anti-obesity drugs such as lorcaserin (selective serotonin 2c [5-HT$_{2c}$] inhibitor) and phentermine/topiramate ER reduce hyperglycemia in patients with T2DM. Glucose-lowering agents such as GLP-1 receptor agonists and SGLT-2 inhibitors also reduce body weight. The functional overlap between glucose-lowering and weight-reducing pharmacotherapies is only likely to increase as novel agents with multiple mechanisms of action are being developed (e.g., dual or triple acting incretin agonists). Both classes of drugs, glucose-lowering agents and anti-obesity medications, are known to impact cardiovascular risk. Therefore, establishing the cardiovascular risk/benefit profile of novel glucose-lowering therapies and anti-obesity medications is critical so treatment benefits can be effectively balanced against the increased risk of cardiovascular events.

Historical Perspective on Assessing Cardiovascular Safety

Historically, the cardiovascular safety profiles of novel glucose-lowering therapies and anti-obesity medications have not been rigorously established prior to entering the market, increasing patient exposure to cardiovascular risk and the possibility of death, stroke, and significant morbidity (e.g., amputation).

Prior to widespread implementation of late-stage, well-controlled, cardiovascular outcome trials (CVOT), assessment of cardiovascular risk for glucose-lowering agents was often limited in phase 2 and 3 studies. The trials were not required to include or adjudicate cardiovascular endpoints, often enrolled relatively young healthy subjects, and were too short to observe a large number of cardiovascular events that would have allowed for an accurate estimation of risk. These shortcomings led to the cardiovascular safety of glucose-lowering agents, including insulin, being heavily debated. Today, many of the common glucose-lowering agents that are prescribed in a clinical setting have limited data pertaining to their cardiovascular effects. For example, metformin is the accepted first line therapy for glucose reduction, but its cardiovascular safety has never been assessed in a large randomized clinical trial (RCT) that is designed and powered for cardiovascular endpoints. The implementation of CVOTs for anti-obesity drugs has lagged behind glucose-lowering therapies, despite the known cardiovascular toxicity profiles of earlier weight-loss medications (e.g., aminorex, fenfluramine and dexfenfluramine, phenylpropanolamine, sibutramine). To date, sibutramine is the only anti-obesity medication

that has been evaluated in a CVOT, and it was withdrawn from the market in Europe and the United States due to concerns about cardiovascular toxicity.

Current Regulatory Environment for Development of Glucose-Lowering Therapies and Anti-Obesity Medications

The FDA has implemented strict guidance for establishing the cardiovascular safety of novel therapies; however, there is no industry wide consensus as to the standard methods that should be employed in assessing the cardiovascular safety of novel glucose-lowering therapies and anti-obesity medications.

The key principles of the FDA guidance, released in 2007, for establishing the efficacy and safety of novel anti-obesity medications is summarized in Table 1. While the FDA does not specifically require CVOTs for new anti-obesity drugs, all the recently approved anti-obesity drugs, except for liraglutide (CVOTs already exist), have been required to conduct cardiovascular risk assessments. In the context of glucose-lowering therapies, guidance on the FDA expectations for a CVOT was released in 2008 and is summarized in Table 2. The European Medical Agency (EMA) adopted similar principles in a 2012 guideline but did not specify the boundaries of acceptable risk. The approach that the EMA adopted recognized that safety studies are complicated by the comorbidities and concurrent medications that are often present in patients with T2DM. Therefore, they required that Sponsors collect non-clinical data from relevant animal models and sufficient clinical data from phase 2 and 3 studies or a single long-term CVOT.

Table 1. Key points from the FDA industry guidance for Anti-Obesity Medications

Key Points of the FDA Industry Guidance for Anti-Obesity Medications
An obesity drug is considered effective if pre-specified weight loss criteria are met after one year of treatment compared to placebo. Statistical significance must be demonstrated for mean weight loss ≥5% between the active- and placebo-treated groups; the percentage of patients who lose ≥5% of their body weight must equal or exceed 35% and be approximately double the percentage in the placebo group.
While the target treatment population is patients with a BMI ≥30 kg/m^2 or ≥27 kg/m^2 with other cardiovascular risk factors, CVOTs for anti-obesity drugs should include patients with extreme obesity, defined as a BMI ≥40 kg/m^2.
Studies should include patients with T2DM who may not respond as well to anti-obesity drugs.
Studies should seek to randomize approximately 3,000 patients to doses of active drug and no fewer than 1500 subjects should be on placebo for 12 months. This sample size is recommended to provide 80% power to rule out with 95% confidence an approximately 50% increase in the incidence of adverse events occurring at a rate of 3% in the placebo group.
Anti-obesity drugs targeting the 5-HT system (e.g., 5-HT2 receptor) should prospectively evaluate the risk for cardiac valvulopathy using serial echocardiography.

Table 2. Key points from the FDA industry guidance for COVT for Glucose-Lowering Therapies

Key Points of the FDA Industry Guidance for CVOT for Glucose-Lowering Therapies
Cardiovascular endpoints should be prospectively established and adjudicated by a blinded committee for all phase 2 and 3 studies. Cardiovascular events should include mortality, myocardial infarction, stroke, hospitalization for acute coronary syndrome, and urgent revascularization procedures. Sponsors should ensure that phase 2 and 3 studies are designed and conducted so that a meta-analysis can be performed on completion.
To ensure sufficient endpoint events, phase 2 and 3 studies should include subjects at higher risk for cardiovascular events, such as those with relatively advanced type 2 diabetes, elderly patients, and subjects with degrees of renal impairment.
A minimum of 2 years' cardiovascular safety data must be provided.
Sponsors should explore similarities and/or differences in subgroups, e.g. age, sex, race, if possible.
To satisfy the statistical guidelines, the analysis of cardiovascular events may include a meta-analysis of all placebo-controlled trials, add-on trials, and active-controlled trials. Alternatively, a single, large, safety trial may be conducted alone, or added to other trials.
Sponsors should compare the incidence of important cardiovascular events occurring in the patients treated with the investigational product compared to the control group. The upper bound of the 95% confidence interval (CI) for the estimated risk should be <1.8.
If the premarketing application shows the upper bound of the 95% CI for the estimated increased risk of cardiovascular events is between 1.3 and 1.8, and the overall risk analysis supports approval, a postmarketing cardiovascular study is generally necessary to show that the upper bound of the 95% CI for the estimated risk is <1.3.
If the premarketing application contains clinical data to show that the upper bound of the 95% CI of the estimated risk is <1.3, and the overall risk analysis supports approval, a postmarketing cardiovascular study may not be necessary.

CVOT Outcomes and Limitations

Since the FDA issued the 2008 guidance, there have been 17 large, prospective, randomized CVOTs performed for glucose-lowering therapies that have enrolled >140,000 subjects. Of the completed CVOTs, all have succeeded in excluding an unacceptable level of cardiovascular risk across three different classes of glucose-lowering therapies (GLP-1 receptor agonists, SGLT inhibitors, and DPP-4 inhibitors). There has been one CVOT conducted for an anti-obesity medication (sibutramine) and three that have been initiated.

A well-designed CVOT provides important information about the cardiovascular safety profile of a given glucose-lowering therapy or anti-obesity medication. However, the results of CVOTs across a class of drugs can still be conflicting. For example, the LEADER (liraglutide) and SUSTAIN-6 (semaglutide) trials showed cardiovascular benefits for GLP-1 receptor agonists, but the ELIXA (lixisenatide) and EXSCEL (exenatide) trials did not show a similar reduction in cardiovascular risk. The reasons for the discrepancy in the trial results are still unclear,

making it difficult to draw conclusions about the cardiovascular profile of GLP-1 receptor agonists as a class. Similarly, while the beneficial cardiovascular profiles of saxagliptin and canagliflozin are paradigm changing results that may expand the potential indications for SGLT-2 inhibitors, findings from the EMPA-REG OUTCOME and CANVAS programs are not completely consistent. The EMPA-REG OUTCOME trial showed a reduction in both all-cause mortality and cardiovascular death with empagliflozin that was not reproduced in the CANVAS program. However, a beneficial cardiovascular profile for SGLT-2 inhibitors as a class is supported by observational data from the CVD-REAL study (300,000 patients in six countries), which found that SGLT-2 inhibitors (dapagliflozin, canagliflozin, empagliflozin) reduced hospitalization for heart failure by 39% and the composite endpoint heart failure and death from any cause by 56%. Additional data from the ongoing DECLARE-TIMI 58 trial, the largest primary prevention trial initiated to date with SGLT-2 inhibitors, may help definitively address the cardiovascular class effects of SGLT-2 inhibitors when it completes in 2019. Based on the CVOT results in T2DM patients, SGLT-2 inhibitors are being assessed in two trials in heart failure patients, EMPEROR HF (empagliflozin) and DAPA HF (dapagliflozin).

General Considerations for Designing an Early Phase Cardiovascular Safety Study

Robust early phase testing to establish the cardiovascular risk/benefit profile of a glucose-lowering therapy or anti-obesity medication can inform important go/no go clinical decisions before extensive, expensive phase 3 or 4 CVOTs are initiated. There are several new anti-obesity medications in the pipeline that target the methionine aminopeptidase-2 (MetAP2) pathway, melanocortin-4 receptor (MC4R), and monoamine reuptake inhibitor pathway. In early phase studies these molecules have cardiovascular toxicity in some patient populations. For example, beloranib, a first generation MetAP2 inhibitor, was discontinued following thrombosis related deaths in obese patients with Prater-Willi Syndrome, and tesofensine, a triple monoamine reuptake inhibitor, has been shown to increase heart rate and blood pressure at the highest dose tested in phase 2 trials.

Implementing an integrated approach designed to assess the cardiovascular risk/benefit of a glucose-lowering therapy or anti-obesity medication during early clinical development is crucial. General considerations for the study design of an early phase cardiovascular safety study include the type of study and study population.

Type of Study – In the context of the FDA guidance, a CVOT is designed as a non-inferiority study; meaning the intention of the trial is to definitively show that the upper boundary of the 95% CI of the estimated increased cardiovascular risk is <1.3. A CVOT is not intended to induce a difference in glycemic control or weight-loss between the treatment arms. In fact, the CVOT aims to minimize differences between treatment arms by permitting adjustment to the treatment regimens that subjects in the comparator group receive so that glycemic control and body weight are comparable between treatment arms. Similar concerns may be applicable to early phase cardiovascular safety studies.

Study Population – A CVOT is inherently based on the number of the cardiovascular events observed. Therefore, the subject population recruited to participate tends to be at higher risk for cardiovascular events. Subjects enrolled in CVOTs are also typically taking medications such as statins, antihypertensive drugs, and antiplatelet drugs that are prescribed to manage comorbidities associated with T2DM and obesity in accordance with the current standard of care. The patient population enrolled in a CVOT can limit the generalizability of the findings, as they differ from the general population encountered in a typical clinical setting. Therefore, routine clinical use studies can provide important data to complement a rigorous CVOT. In early phase cardiovascular safety studies, it may be beneficial to include a similar study population, but use established surrogate markers for cardiovascular events, thereby reducing the number of subjects required and the duration of the study.

Early Phase Cardiovascular Safety Study Endpoints

Robust early phase cardiovascular safety testing can utilize a wide range of sensitive early biomarkers to identify cardiovascular safety signals. Early phase cardiovascular safety studies can include invasive or non-invasive exploratory endpoints and biomarkers. Advances in the field of cardiology have led to new technology to assess the endovascular, vascular, and structural facets of the cardiovascular system. In general, the approach selected should account for the molecular properties of the drug, the biodistribution of the drug, and the half-life of the drug in the cardiovascular system. Most drugs transit through or reside in the circulatory system so "on" or "off" target cardiovascular effects are expected. The methodologies that can be used in early phase cardiovascular safety studies include the following:

Major Adverse Cardiovascular Events – The primary outcomes for all the major CVOTs have been either 3- or 4-point major adverse cardiovascular events (MACE) endpoints (Table 3). The field is not in agreement that hospitalization for unstable angina should be included in the 4-point MACE endpoints. The concerns raised regarding this endpoint have been related to diagnostic imprecision and, since diabetes drugs have little impact on this endpoint, the potential to bias the results of a trial to null. While an early phase cardiovascular safety study will not be powered to detect differences in the incidence of these events, they may be included as adverse events of special interest.

Table 3. Major Adverse Cardiovascular Events Assessed in CVOTs for Glucose-Lowering Therapies

Primary Major Adverse Cardiovascular Events (MACE) Endpoints	
3-point MACE Endpoints	**4-point MACE Endpoints**
Cardiovascular death	Cardiovascular death
Non-fatal myocardial infarction	Non-fatal myocardial infarction
Non-fatal stroke	Non-fatal stroke
	Hospitalization for unstable angina

Adopted from: Krentz et al. 2017

Endothelial function assessments – Given the surface area of the endothelium in the vasculature, it is virtually guaranteed that the endothelium will be exposed to the drug. Methods of measuring the integrity of endothelial function include chemical and non-chemical flow mediated-dilation, magnetic resonance imaging (MRI)-targeted differentials in oxygenation, flow fractional reserve using pressure wires in specific coronary or peripheral vessels, and external flow-mediated dilation (e.g., ultrasound).

Vessel stiffness – The endothelium releases nitric oxide (NO), which has vasodilator properties that can affect the stiffness of the vasculature. The relaxation or stiffness of the vasculature reflects local factors (e.g., NO release) and systemic factors (e.g., adrenaline). Vasodilation can be measured using pulse wave velocity (an independent predictor of vascular events), blood pressure measurements with 24-hour monitoring or ambulatory systems (predictive of vascular mortality), and telemetry to measure intra-arterial blood pressure.

Coagulation responses – Novel compounds encounter the coagulation system during transit in the vessels. Effects on coagulation can be measured by assessing acute consequences (e.g., bleeding), coagulation times, D-dimer levels, platelet count, anti-thrombin levels, protein C/S, and the international normalized ratio (INR). This is particularly important for drugs that have affinity to calcium ions, platelet membrane-phospholipids, serine proteases, tissue factors, and vitamin K. Identification of drugs thought to have (or that have) acute thrombo-ischemic or hemorrhagic phenotypes in phase 2 trials can inform go/ no go decisions.

Functional imaging – Imaging studies can be used to characterize the phenotypes of arteries, veins, and the heart, and the results may be useful for understanding the effects of drugs in other vascular beds. Drugs that are like insulin, or have growth properties, may overlap with cellular proliferation pathways in vascular beds and exacerbate pre-existing conditions like atherosclerosis and vascular inflammation. Specific methods include intravascular ultrasounds, optimal coherence tomography, ultrasonography, MRI, positron emission tomography (PET), exovascular ultrasound, and computed tomography (CT). The imaging modalities can be combined or used singly to meet clinical needs and endpoints. Functional imaging studies are especially useful in phase 2 studies to evaluate the impact of a novel compound in normal anatomy and in the context of pre-existing conditions. Imaging findings can relate to positive or negative impacts that are directly related to approval, no-approval, or withdrawal of products later in development, and support mechanism of action determinations or new indications.

Biomarker studies – Early phase studies should include established biomarkers of cardiovascular function including blood pressure, electrocardiographic QT intervals, heart rate, high-sensitivity C-reactive protein, carotid-intima media thickness, lipid profiles, and body weight. Newer biomarkers to consider include fibrinogen, amyloid A, natriuretic peptides, pentraxin 3, homocysteine, and soluble CD40 ligand. Biomarker profiles can be combined to show clinical benefits/risks and to stratify patients based on the pathogenesis of vascular disease.

Conclusions

T2DM and obesity are both complex, interrelated diseases that are related to cardiovascular health, and the functional profiles of new glucose-lowering therapies and anti-obesity medications are overlapping. Therefore, rigorous cardiovascular safety studies are crucial during early phase development of these drugs. Early implementation of an intentional cardiovascular program beginning during phase 1 and 2 development can provide valuable information to inform later clinical decisions, improve the likelihood of success, avoid expensive multi-year delays in development, minimize the risks to patients, and minimize the need for expensive phase 3 or 4 safety studies in response to regulatory requests. As the evidence base for assessing cardiovascular safety continues to evolve, a greater focus on early phase development offers a logical approach to minimizing the risks of new glucose-lowering and weight-reducing medications.

Looking Ahead

To thoroughly characterize the cardiovascular profile of a novel drug in early phase studies, the study design should account for the molecular properties of the compound, drug pharmacokinetics, preclinical data, and patient characteristics specific to the target population. If possible, advances in precision medicine should be utilized to select or stratify the subjects enrolled in early phase cardiovascular studies based on their genetic, epigenetic, and proteomic profiles. Integrating these components into drug development programs and business strategies will help inform opportunities for label exploration or expansion, and the decision whether to pursue further development of a new glucose-lowering therapy or anti-obesity medication. A science-driven exploration

of the cardiovascular safety profile of novel drugs may contribute to healthcare innovation by generating more complete data to ensure that safe and effective therapies will be available for patients with diabetes, obesity, and associated metabolic disorders.

Further Reading

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As Senior Research Fellow at ProSciento, Prof. Krentz's research has involved investigator-initiated research in diabetes and cardiometabolic disorders. In addition to original articles, reviews and book chapters he has authored or edited a number of well-received textbooks on diabetes and cardiovascular disease including and *The Metabolic Syndrome and Cardiovascular Disease* (2007), *Drug Therapy for Type 2 Diabetes* (2013) and *Translational Research Methods for Diabetes, Obesity and Cardiometabolic Drug Development* (2015). Previously, he was Professor of Endocrinology & Metabolism at the University of Buckingham, UK. Prof. Krentz serves on the editorial boards of a number of scientific journals. He is the founding Editor-in-Chief of *Cardiovascular Endocrinology*.

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