Closer Look

European Association for the Study of Diabetes (EASD) 51st Annual Meeting

September 13-18, 2015: Stockholm, Sweden - Full Report - Outcomes Trials - Draft

Executive Highlights

The presentation of positive results from EMPA-REG OUTCOME (CVOT for Lilly/BI's Jardiance [empagliflozin]) represented the absolute high point of the week, and speakers and audience members alike appeared taken aback by the unexpected benefit and the secondary benefits in particular. The mechanism of cardioprotection emerged as one of the biggest unanswered questions from the trial. The consensus among speakers was that the diuretic effect was the most likely driver of benefit, as the expected culprits (improvements in blood pressure, weight, or lipids) would be unlikely to produce such a dramatic immediate effect on mortality and heart failure with no impact on non-fatal MI or stroke. Speakers seemed to agree that an SGLT-2 inhibitor class effect is the most likely explanation for the positive results, though they repeatedly cautioned against over-generalizing from the results of one trial. Our expectation is that guidelines committees and payers will want to wait for results from the other SGLT-2 inhibitor CVOTs before designating the class as a standard second or even first line option. However, the results should certainly have some impact on prescribing patterns and will almost certainly help Jardiance gain some commercial and reimbursement ground against its more established competitors.

Speakers offered mixed opinions on the implications of the EMPA-REG OUTCOME results for broader CVOT policy. Several, including Dr. Sattar, Dr. Marc Pfeffer (Brigham and Women's Hospital, Boston, MA), and Dr. Hertzel Gerstein (McMaster University, Hamilton, Ontario, Canada) spoke strongly in favor of outcomes trials, and Dr. Silvio Inzucchi (Yale University, New Haven, CT) went so far as to state that he is now prepared to completely revise his previous opposition to these FDA-mandated studies. However, other speakers including Dr. Lars Rydén (Karolinska Institute, Stockholm, Sweden), Dr. Steve Bain (Swansea University, UK), and Dr. Rury Holman (University of Oxford, UK) took a more critical view, noting that many of the frequently-cited limitations (short duration, disproportionately high-risk populations, etc.) still apply. We acknowledge that EMPA-REG OUTCOME did reveal an unexpected and clinically meaningful benefit that may have remained unknown without the FDA requirement to conduct an outcomes trial. However, we feel that there are still many valid critiques of the current approach, and we hope to see discussion in the coming years about potential modifications that could lead to a more favorable cost-benefit ratio and ensure that these trials are answering the most relevant clinical questions.

Below is our complete coverage of Outcomes Trials from EASD 2015. Titles highlighted in blue are new additions that were not mentioned in our daily updates from Stockholm, and those highlighted in yellow represent what we felt were the most notable talks of the meeting.

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Outcomes Trials

Symposium: Results of the EMPA-REG OUTCOME Study

EFFECTIVENESS

Christoph Wanner, MD (University of Würzberg, Germany)

Dr. Christoph Wanner presented the results for A1c and other surrogate parameters in EMPA-REG OUTCOME, which were consistent with those seen in previous trials of SGLT-2 inhibitors. After the initial 12-week period when investigators were not allowed to alter glucose-lowering medications, placebo-adjusted A1c reductions were 0.54% and 0.6% with the 10 mg and 25 mg doses of empagliflozin, respectively. The difference between groups narrowed after week 12, when investigators could adjust medications at their discretion. At the end of the 206-week study period, the placebo-adjusted reductions were 0.24% and 0.36%, reflecting the goal of achieving glycemic equipoise between groups. Both doses of empagliflozin led to ~2 kg placebo-adjusted weight loss and a ~2 cm reduction in waist circumference shortly after study initiation that were largely sustained throughout the trial. Empagliflozin also produced a sustained ~4 mmHg placebo-adjusted reduction in systolic blood pressure - Dr. Wanner cryptically noted that he would leave it to the audience to make judgments on the magnitude of that effect. Diastolic blood pressure initially decreased by ~1.5 mmHg with empagliflozin vs. placebo, but the difference had essentially

disappeared by the end of the study. Heart rate (measured by ECG and in outpatient visits) was stable throughout the trial and comparable between groups. LDL cholesterol increased slightly with empagliflozin from the beginning of the trial, consistent with other SGLT-2 inhibitor studies. HDL also increased with empagliflozin such that the HDL/LDL ratio remained balanced between groups.

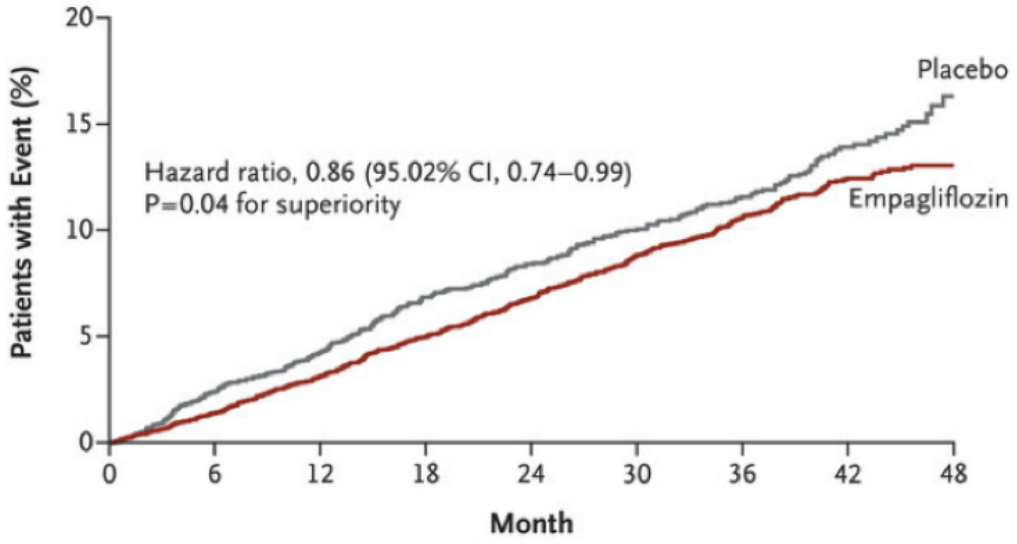
OUTCOMES

Silvio Inzucchi, MD (Yale University, New Haven, CT)

Clearly enjoying himself, Dr. Silvio Inzucchi presented the much-anticipated primary results from the trial, building up the suspense for each finding by pausing dramatically before the Kaplan-Meier curves slowly appeared, often to gasps and applause from the audience.

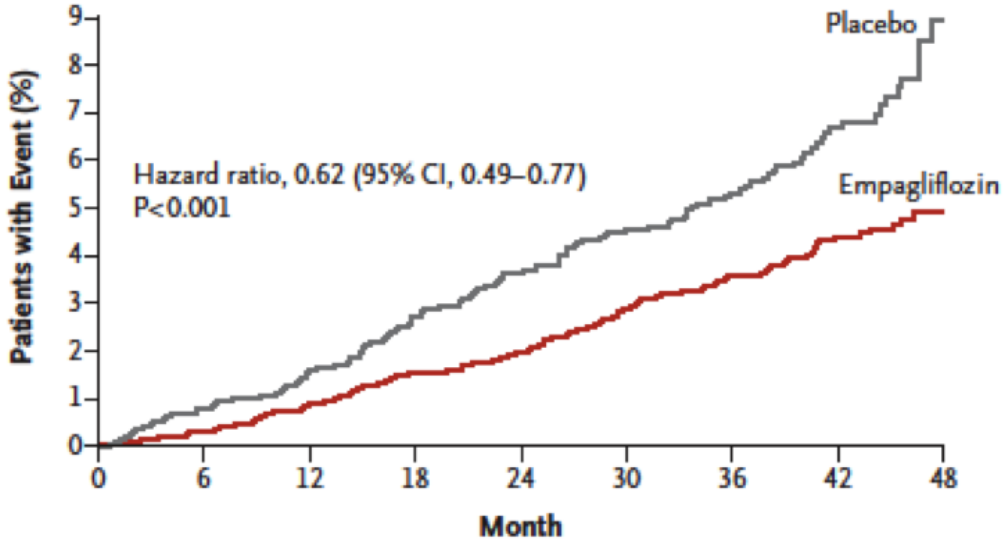
- **Primary outcome:** The hazard ratio for the primary outcome of three-point MACE (non-fatal MI, non-fatal stroke, and CV death) was 0.86 (95% CI = 0.74-0.99), translating to a 14% risk reduction that just met the threshold for statistical significance (p=0.038 for superiority; p<0.001 for non-inferiority). Dr. Inzucchi noted that the curves began to diverge after only about three months, which he described as very unusual for a cardiovascular trial. The results were consistent between the two empagliflozin dose groups (10 mg and 25 mg) with a hazard ratio of 0.85 for both, though the p-values did not reach statistical significance because of the smaller number of patients in each group. On-treatment and per-protocol analyses to test the robustness of the results found the same results.
- **Individual components:** It soon became clear that the overall risk reduction was driven entirely by a 38% reduction in CV death (HR = 0.62; 95% CI = 0.49-0.77; p<0.0001), which drew the first applause and gasps from the audience. The effect was again consistent between the individual dose groups, and in this case significance was maintained despite the smaller number of patients. There was no significant difference in non-fatal MI (HR = 0.87; 95% CI = 0.70-1.09; p= 0.22) or non-fatal stroke (HR = 1.24; 95% CI = 0.92-1.67; p = 0.16) between groups. Dr. Inzucchi offered some reassurance about the numerical increase in stroke, noting that the majority of events occurred more than 90 days after discontinuation of treatment and that the hazard ratio was much closer to unity (1.04) in a prespecified on-treatment analysis that included events only up to 30 days after discontinuation.
- **Key secondary outcome:** Adding hospitalization for unstable angina (which was balanced between groups) to the primary composite endpoint pushed the results just below the threshold for statistical significance for superiority (HR = 0.89; 95% CI = 0.78-1.01; p<0.001 for non-inferiority; p=0.08 for superiority).
- **Subgroup analyses:** There was some heterogeneity in the subgroup analyses for the primary endpoint, with nominal differences based on age (more of an effect for people under 65) and A1c (more of an effect for people with A1c<8.5%). However, Dr. Inzucchi stressed that no interactions met the threshold for statistical significance (p=0.0022) in this analysis. Results of the subgroup analyses for CV death were much clearer, with absolutely no heterogeneity and a clear benefit for all groups analyzed.
- **Heart failure:** Dr. Inzucchi really built up the suspense for this endpoint, prefacing the results with a discussion of the enormous relevance of heart failure for patients with diabetes and the ongoing controversy over the DPP-4 inhibitor class. The audience once again burst into applause when the highly significant 35% risk reduction was presented (HR = 0.65; 95% CI = 0.50-0.85; p=0.002). The results for the individual dose groups were similar, though the curves were not quite as superimposable as those for CV death.
- **All-cause mortality:** Dr. Inzucchi closed on a high note with the results for what he described as "probably the most important outcome." Results demonstrated a 32% reduction in all-cause mortality with empagliflozin (HR = 0.68; 95% CI = 0.57-0.82; p<0.001) with no difference between the two doses.

A Primary Outcome

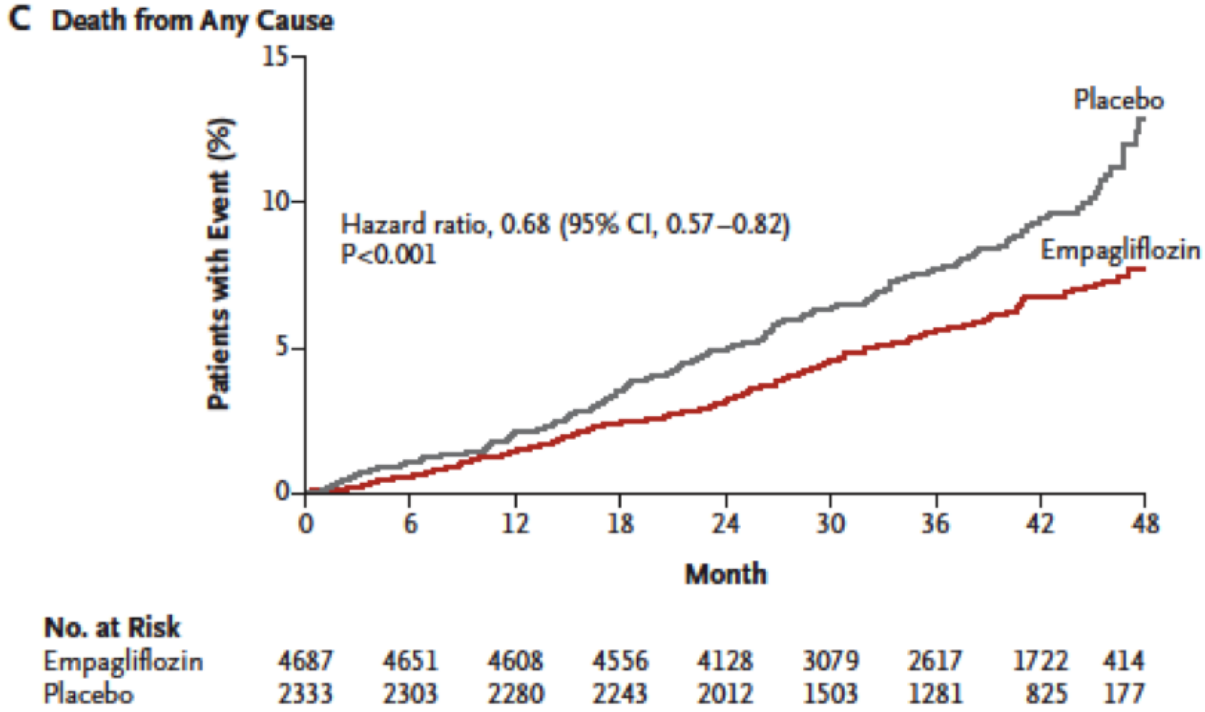


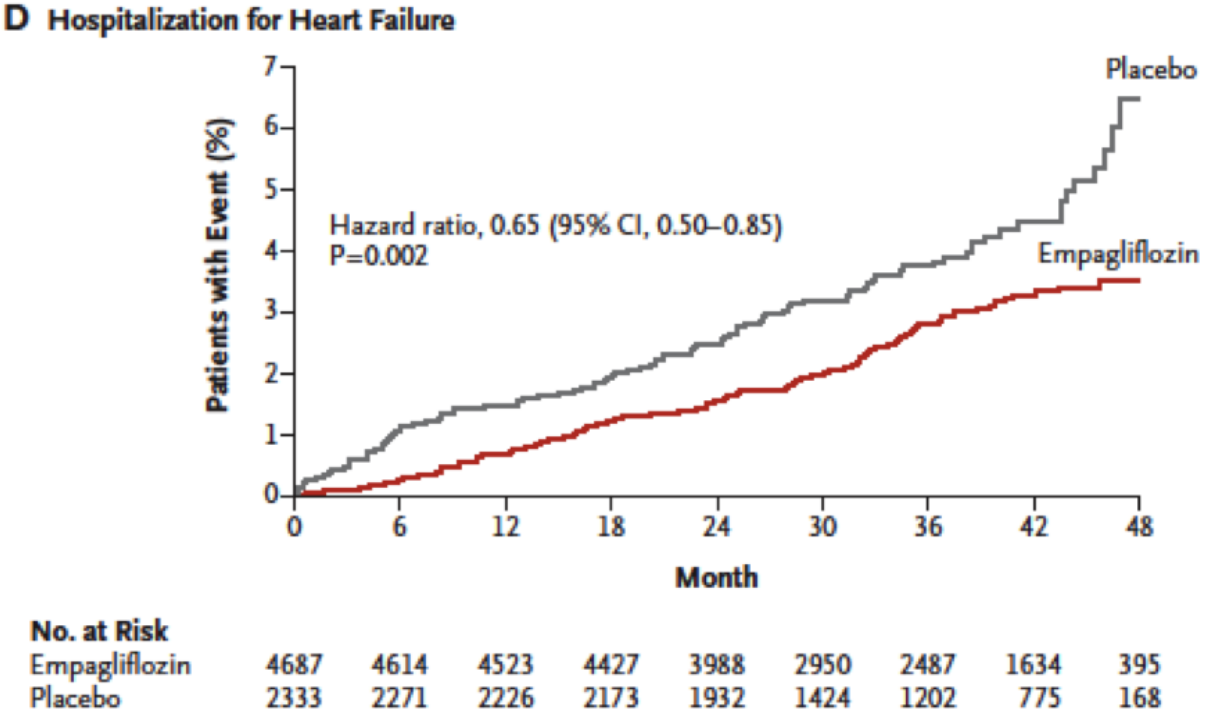
No. at Risk									
Empagliflozin	4687	4580	4455	4328	3851	2821	2359	1534	370
Placebo	2333	2256	2194	2112	1875	1380	1161	741	166

B Death from Cardiovascular Causes



No. at Risk									
Empagliflozin	4687	4651	4608	4556	4128	3079	2617	1722	414
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177





SAFETY

David Fitchett, MD (St. Michael's Hospital, Toronto, Ontario, Canada)

Dr. David Fitchett presented the results for adverse events, which were generally reassuring. There was a slight increase in drug-related adverse events with empagliflozin, largely due to increased genital infections, which occurred in 6.4% of all patients and 10% of female patients on empagliflozin vs. 1.8% and

2.6%, respectively, with placebo. There was no difference in serious adverse events between groups. There was no increase in urinary tract infections with empagliflozin, though there was a very slight increase in discontinuation due to such infections. Hypoglycemia was common (28%) in both groups, reflecting the fact that half the participants were on insulin. There was no increase in overall hypoglycemia or hypoglycemia requiring assistance with empagliflozin vs. placebo, including when patients were stratified based on insulin therapy. Notably, given recent concerns, there was no increase in DKA or bone fractures with empagliflozin. There was also no increase in acute kidney injury, events associated with volume depletion, venous thrombotic events, hepatic injury, or hypersensitivity. There was a 4% absolute increase in hematocrit and a 0.9 g/l increase in hemoglobin with empagliflozin, which Dr. Fitchett described as a result of the drug's osmotic diuretic effect. There was no difference in serum creatinine, eGFR, or electrolytes between groups. Overall, Dr. Fitchett stated that empagliflozin appeared to be well tolerated, with the only risk being an increase in genital infections that rarely resulted in discontinuation.

COMMENTATOR

Hertzel Gerstein, MD (McMaster University, Hamilton, Ontario, Canada)

Dr. Hertzel Gerstein provided valuable context for the EMPA-REG OUTCOME results, endorsing the robustness of the study, emphasizing the value of large outcomes trials, and offering some hypotheses as to the mechanism of benefit. He argued that "this trial has really performed well," noting that it met all of his criteria for a useful, reliable outcomes study. He also described it as a "perfect case in point" for why large outcomes trials are necessary and cannot be replaced with large epidemiological studies or meta-analyses of small RCTs. While the mechanism of benefit remains unknown, Dr. Gerstein suggested that a diuretic effect was the most likely driver based on comparisons to past trials, though it could also be a combination of multiple factors. One of Dr. Gerstein's endorsements of the trial was that it raised more questions than it answered, and he outlined several of those questions during the talk, mostly related to the mechanism of action and the generalizability of the results. In terms of the clinical implications, he predicted that the benefit is likely to be a class effect and suggested that empagliflozin could become the first-line treatment for middle-aged people with type 2 diabetes at high cardiovascular risk.

- **EMPA-REG OUTCOME met all of Dr. Gerstein's criteria for a good outcomes trial:** it had a good protocol, answering an important question in a high-risk population; it had high adherence and event ascertainment, with a higher event rate than anticipated; the investigators delivered a clear analysis and presentation of the results; and it "definitely" raised more questions than it answered. As he summed it up, "this trial has really performed well."
- **Dr. Gerstein described EMPA-REG OUTCCOME as a "perfect case in point" for why large outcomes trials are needed.** He argued that the claims (fairly widespread in the field in recent years) that large outcomes trials for diabetes drugs are not necessary or valuable are "really unfounded." He stressed that relying on a drug's mechanism of action to predict its effects is not sufficient, as "biology can be used to justify any findings." As in past talks, he expressed skepticism about the use of large epidemiological studies in place of randomized trials, arguing that the results will always be confounded since it is impossible to adjust for confounders you aren't aware of. He also cast doubt on the validity of meta-analyses of small RCTs that are not powered to evaluate outcomes, noting that the biases present in each individual study are only compounded when the results are combined. Few would argue against large, randomized outcomes trials as the gold standard of evidence; the main question facing the diabetes field is whether the information gained from such trials as they are currently designed is worth their substantial cost.
- **Dr. Gerstein suggested that empagliflozin's diuretic effect was the most likely driver of benefit, though it could also be a combination of multiple factors.** He convincingly argued through comparisons to other cardiovascular outcomes trials that the immediate, dramatic effect on mortality and heart failure seen in this study was not consistent with a benefit driven by improvements in blood pressure or lipids, which typically takes at least six months to a year to become evident. The lack of an effect on stroke makes it especially unlikely that the improvement was driven by blood pressure, which we had predicted would be the most likely mechanism. Dr.

Gerstein also suggested that the improvement was very unlikely to be a glucose effect, as the A1c difference between groups was too small and the benefit too immediate. Similarly, he suggested that weight loss was not the culprit, as there is currently no evidence linking weight loss to CV risk reduction and the difference between groups was not huge. He did note that past trials evaluating the effect of diuretics in patients with a history of heart failure have shown an effect on mortality almost immediately after randomization, suggesting that a similar mechanism could be at work here.

- **Dr. Gerstein outlined several important questions raised by the results:**
  - Are the findings generalizable to all patients with type 2 diabetes?
  - Why were the results different for different MACE components?
  - Does empagliflozin or other SGLT-2 inhibitors reduce ischemic heart disease or stroke over the long term?
  - What is responsible for the benefits?
  - Why did the benefits appear so quickly?

Corporate Symposium: EMPA-REG OUTCOME - Implications for Management of Patients with Type 2 Diabetes (Sponsored by Lilly/BI)

PANEL DISCUSSION

Lars Ryden, MD, PhD (Karolinska Institute, Solna, Sweden), Sanjay Kaul, MD (Cedars-Sinai Heart Institute, Los Angeles, CA), Lawrence Leiter, MD (St. Michael's Hospital, Toronto, Canada), Naveed Sattar, MD (University of Glasgow, UK)

Q: Should SGLT-2 inhibitors replace metformin as the first choice for type 2 diabetes with high cardiovascular risk?

Dr. Lawrence Leiter: There's a lot to include in this answer. These are fantastic results that show a dramatic benefit in the population that was studied. What was seen was a benefit in people with known cardiovascular disease. What is yet to be shown, though there are other SGLT-2 inhibitor trials ongoing, is the benefit in people without known cardiovascular disease. Also, the drug was given on a background of metformin therapy, so we know it has a benefit on top of metformin. It's premature to replace metformin with SGLT-2 inhibitors.

Dr. Naveed Sattar: Most of us were blown away by the results. I don't think anyone could have predicted the results. It is a bit confusing - the difference between dying from CV event and nonfatal events. Things that prevent nonfatal disease is lipid lowering and blood pressure and metformin is part of that. Metformin is cheap, safe, and it works.

Dr. Sanjay Kaul: It's too premature to jump to this particular drug as first-line therapy. Metformin was tested in new onset diabetes and we haven't tested this in that. The mortality benefit found is profound and early but we need to admit that it's unexpected and unprecedented. At first glance, it seems too good to be true. That said, there are cogent reasons as to why I don't believe this is an implausible benefit. It was statistically persuasive, based on a large number of events, and was seen with both doses; so there was internal consistency. Thus, it wasn't a play of chance. Nonetheless, I would like to see it replicated by another drug within the class.

Dr. Lars Ryden: The trial has been done in certain settings in certain patients. They were treated with many things and the results are based on adding this on top of other treatments. You have to use clinical experience and skills to choose the patient you're putting on this. Another study will give us an answer to other types of patients.

Q: Many of the other cardiovascular outcome trials since December 2008 have addressed patients within 60 days of an index event. EMPA-REG had patients more than two months from a prior cardiovascular event. Did that difference allow a better opportunity?

Dr. Ryden: Maybe. Heart failure was influenced and it takes some time to develop.

Dr. Kaul: For chronic disease, it's very important to carefully choose the time of ascertainment of events. If you enroll patients early after an ACS event, you'll likely get a lot of noise and dilute a potential treatment benefit. The timing of enrollment more than two months after an acute event was quite appropriate..

Dr. Leiter: In the completed ACS studies, none of them included patients right after the event. ELIXA is yet to be published and uses at least 60 days after event. Even EXAMINE used from 15 days on. There just weren't many patients with events that early. It's not that dissimiliar from prior studies.

Q: Can you provide any comments on the finding that most of the treatment benefits were in the age group above 65 years old?

Dr. Ryden: When looking at differences between subgroups, none of them was actually statistically significant. All went in the same direction. We cannot draw conclusions above or below as they were all very consistent. The hazard ratios were narrow or wide depending on the number of people in a specific subgroup. The results are consistent for all patients studied.

Dr. Kaul: Subgroups are tempting, but often treacherous. Prestigious journals are demanding nominal unadjusted interaction p-values that can be potentially misleading.

Dr. Ryden: There was a related question to gender and it's the same answer.

Dr. Sattar: The fact that nonfatal disease didn't change is because we've treated processes for nonfatal disease very well. The process for treating fatal disease is another pathophysiology that we haven't seen.

Dr. Leiter: With regards to MI, remember that it was non-significant but had a 13% reduction. What is remarkable is the CV death benefits that allowed the study to finish with sufficient events.

Q: When thinking about mechanisms of action, was there reduction in the non-diuretic treatment patients?

Dr. Sattar: Could it be diuretic events alone? Probably not. Is it having some kind of diuretic event or background of weight and blood pressure and glucose? I don't know. I don't think anyone has the precise answer.

Dr. Kaul: The mechanism of action is tempting to speculate, but we simply don't know the exact mechanism.

Dr. Ryden: If you look at the rapid onset, SGLT-2 leads to volume depletion, which could unload the heart. There are many other aspects, including less remodeling, less fibrosis, and less coronary vascular stiffness. We need to do very specific trials with this drug to get a more detailed explanation to the mechanisms behind the effect. There certainly will be a number of studies. This study opens up to many thoughts.

Dr. Kaul: We cannot tell what the exact mechanism of action is. What we can tell with some degree of confidence is what it is not related to. It is not a blood pressure effect. Why would stroke go in the wrong direction? It's not related to weight loss. This has never been shown with 2%-3% weight loss. We know this is not a glycemic effect. The glycemic differential is too modest to translate into an outcome benefit. That's all we can say. We could consider a hemodynamic effect or a membrane stabilization effect? Ask yourself: when was the last time a hemodynamic or an antiarrhythmic intervention had such a profound and early treatment benefit? I'm not aware of it.

Dr. Leiter: I'd like to provide a note of caution. The danger in trying to come up with an explanation is that we try to generalize. If it's glucose lowering, then we say that the benefit would be seen with any glucose lowering agent. If it's blood pressure, then we say that for anything. If it's diuretic, then we put everyone on Hydrochlorothiazide. But that's not what the study showed. Empagliflozin showed a dramatic benefit and it's not appropriate to generalize these results to drugs with other mechanisms of action.

Q: Regarding the possibility of a class effect, are any SGLT-2 inhibitors valid in this sense?

Dr. Kaul: What is common to all SGLT-2 inhibitors is a favorable impact on cardiometabolic risk factors. But we saw that the outcome benefit in this trial was unlikely to be attributable to blood pressure lowering, weight

loss, or improved glycemic control. So, the question of whether this is a class effect is now difficult to answer. We need to await the results of ongoing CVOT with other drugs within the class.

Dr. Ryden: Another example is the first study of DPP-4 inhibitors, SAVOR, which showed an increase in heart failure in the group receiving saxagliptin. Subsequent studies did not reveal anything similar eg. in TECOS testing sitagliptin. However, in the DPP-4 inhibitor class of drugs, the molecular structure of each is quite dissimilar. Thus we cannot just say that all drugs in the class is safe even if I personally believe that the findings in SAVOR was a play of chance

Dr. Leiter: Despite everyone dumping on FDA and EMA regulations, we don't need to wait five years now to see what happens with other studies underway. We'll have an answer in a few years.

Dr. Sattar: If you asked us to bet, we'd probably say yes. But we have doubt in our mind about whether or not it's drug specific, so we can't say until other trials complete.

Q: For the first month, treatments could not be changed. There was a clear drop in A1c. Would this affect the blinding of the study?

Dr. Ryden: It's a good question. If you administer a drug that is glucose lowering it has an effect. That does not necessarily mean it flaws the results especially since the impact was relatively small.

Dr. Leiter: I don't think so. What was seen in the EMPA-REG outcomes was seen in previously completed DPP-4 and GLP-1 trials. There was a very similar delta at three to four months, which gradually diminished over time. In each of these studies, investigators were encouraged to treat per local guidelines. The average A1c was still far above what we would recommend. I don't think it was a result of glycemic benefit.

Dr. Sattar: The end result was 0.3% for A1c, which was almost identical to previous trials. It cannot be that.

Dr. Ryden: A total of 7,000 patients were recruited at almost 600 centers. The responsible physicians cared for the patients as they were instructed and each of them had of course a limited number increasing the chance to guess which arm their patients were allocated to.

Dr. Kaul: It would be a mistake to interpret these results as a validation of the hypothesis that improved glycemic control results in improved cardiovascular benefits. This is simply not what the study shows.

Q: Because the heart failure outcome may have accomplished an important role, what happened with BNP? Was this not yet analyzed?

Dr. Sattar: When thinking about the patients beyond those studies - beyond people with diabetes and existing vascular disease - people with a high risk of heart failure may have a role. Their BNP may have a role. BNP is an excellent predictor of cardiovascular events. That analysis needs further interrogation.

Q: The Kaplan-Meier curves for MACE diverge almost immediately and then are parallel. For deaths, they diverge and continue. Does that mean strokes and MI increase after six months?

Dr. Kaul: The KM curve for stroke shows delayed separation not in favor of empagliflozin. The ITT hazard ratio was 1.24 for nonfatal stroke, so that's a potential concern.

Q: Would it be interesting to analyze people with risk factors for MACE but no previous cardiovascular events?

Dr. Leiter: In DECLARE, 60% of participants have multiple risk factors but no previous events so that will help answer that question.

Q: The results adjudicated cause of death and all deaths by treatment. Empagliflozin did not reduce risk of acute MI and stroke. What drove that reduction?

Dr. Rydén: A decrease in heart failure is a probable reason as emphasized during the presentation of the study. Heart failure, particularly of ischemic origin, and diabetes is a very deadly combination.

Dr. Kaul: The 2.2% absolute risk reduction in cardiovascular mortality was driven primarily by unknown cause of deaths that by protocol were classified as cardiovascular followed by sudden cardiac death and

worsening heart failure. This raises an interesting hypothesis of a potential heart failure effect that is ripe for validation in future trials.

Q: What might be the mechanisms for hospitalization for heat failure? You know you get volume depletion. You know if you have a burdened or stiff heart, volume depletion in one way or another would unload that heart. You should also know that in animal experiments, if you look at their structure, they're less fibrotic in the myocardium. Perhaps the vessels dilate easier and preserve the myocardial blood flow reserve.

Dr. Sattar: Many of us have seen the data with this drug and the kidney and something about the cardio-renal axis. There's a recent paper published in the UK that shows that the most common CV presentation that people die from is heart failure. One in five of the most common presentations is heart failure. We have to prevent fatal events to the point we can with lipid lowering drugs.

Dr. Kaul: The risk reduction in mortality seen in EMPA REG OUTCOME trial was virtually double the mortality benefits seen with a recently approved heart failure drug called Entresto which was studied in high-risk patients with systolic heart failure. Entresto impacts the renin angiotensin aldosterone system. So, the effects of empagliflozin might go beyond this.

Dr. Sattar: Ten percent of the patients had known heart failure, but it's possible that many others had subclinical heart failure. We don't know that context.

Dr. Kaul: The obvious next step is validating this finding and determining whether there is a treatment benefit in heart failure in people with and/or without diabetes.

Q: Can anyone explain why hypoglycemia was not increased, as in earlier reported diabetes event trials?

Dr. Ryden: This drug does not cause hypoglycemia.

Dr. Leiter: SAVOR was the only outcomes trial that showed more hypoglycemia. Patients in that trial had entry A1c levels as low as 6.5%. It was patients with a low A1c and on insulin that showed hypoglycemia in SAVOR.

Dr. Sattar: If you're on insulin and showing an A1c of 6.5%, some are in good control, but some are quite sick and losing weight.

Q: What about fractures and osteoporosis?

Dr. Ryden: That has not been analyzed yet.

Q: Dr. Gerstein suggested the possible influence of SGLT-2 on cardiac arrhythmia. I don't think he really said that. He referred to arrhythmia trials, but I don't think so?

Dr. Sattar: He did say that, I think.

Dr. Kaul: There is a laundry list of potential reasons. When you see "multifactorial" or "multidimensional" in a journal like the *New England Journal of Medicine,* it's usually a euphemism for we don't know.

Q: What about use of SGLT-2s if the GFR is <45? Are you concerned about off-label prescriptions for patients older than 60 years with impaired renal function?

Dr. Ryden: No, according to the outcome of this study.

Dr. Sattar: It would be nice to see the microvascular outcomes as well.

Dr. Leiter: With impaired renal function, efficacy falls off. But the effect on blood pressure seems to be the same.

Q: What about the imbalance between men and women? There were more males than females in the study.

Dr. Ryden: The disease which made patients available for the study is much more common in men. There was no imbalance in events between men and women. The subgroups all went in the same direction and magnitude. You can use the drug in both genders.

Q: Was QT interval influenced?

Dr. Ryden: We don't know yet. But this drug does not act that way.

Q: How does randomization of empagliflozin and placebo influence statistical calculations?

Dr. Ryden: That was discussed by the study statistician. It is a perfectly fine way of looking at events.

Q: How many patients had new heart failure and how many had worsening heart failure? It will probably come later on, but is not yet known.

Dr. Kaul: We don't have systematically collected information on heart failure.

Dr. Sattar: This is in part because we didn't expect these results. It's a hypothesis generating observation that needs to be validated.

Q: Should SGLT-2 inhibitors be tested in people without diabetes and heart failure?

Dr. Ryden: If you carefully investigate people with ischemic heart failure, the majority is dysglycemic. If you want to isolate those without any disturbance in glucose, then you have to really screen them with an OGTT. To test the drug in patients with heart failure and diabetes is something that should and reasonably will be done. This can be done in a straightforward, large clinical trial but also in small mechanistic investigations .

Q: Regarding dosing, would you give 10 mg or 25 mg? Or something in between?

Dr. Kaul: I would give 10 mg.

Dr. Kaul: There was no difference in cardiovascular outcomes between the 2 doses. I was underwhelmed by the glycemic difference between the 2 doses. I would start every patient at 10 mg and stop there. In the paper, it was mentioned that dose should be individualized based on glycemic efficacy. However, the outcome benefit is unrelated to glycemic control.

Dr. Leiter: There is a cardiology vs. endocrinology divide here. The cardiovascular benefit was no greater at 25 mg. Looking at the other side of it, the harm was no greater. We know from prior studies with empagliflozin that the higher dose is associated with a little bit more A1c reduction and a little bit more blood pressure reduction. There's a little bit more weight loss. We haven't discussed the kidney, even though there was no dose response with cardiovascular benefits. We want to individualize therapy. If patients are doing well on 10 mg for their cardiovascular needs, there's no need to go up. If you want greater metabolic benefit, then there's no harm in going up to 25 mg.

Dr. Sattar: 10 mg is clearly the starting dose. You get the most bang for the buck. You're pretty much getting 90% of the effect. That's on average. There might be some patients who get additional benefit at 25 mg, but 10 mg works well for the vast majority.

Dr. Ryden: I would go with 25 mg, which was safe. We want to take as much as possible out of the drug. In my practice, we start with 10 mg and follow the patient.

Dr. Sattar: I'm involved in the prevention guidelines. I'm going to have to rewrite some of it based on these results. I suspect other committees will also have to.

Q: What hyperkalemia was observed during the study?

Dr. Ryden: There was obviously no problem with that so you can be assured.

Q: If CV deaths were lowered, doesn't this mean that there should have been a rise in nonfatal MI and stroke?

Dr. Sattar: It's a good point.

Dr. Ryden: If you follow the study population let us say during 20 years, you might find something and you can figure out how long life was prolonged?

Dr. Kaul: It's a legitimate question. We would generally expect patients with diabetes to die mostly from atherothrombotic events. That's why there's a composite of CV death, nonfatal MI or nonfatal stroke. Nonfatal MI is the largest contributor to the composite but there was a modest but not statistically significant benefit. When nonfatal stroke doesn't move in the same direction as CV death, it begs the question whether this composite is really the best outcome for these trials. Perhaps there are other things besides atherothrombotic events such as heart failure, arrhythmic events, etc., which may be equally, if not more, important.

Dr. Sattar: It would be nice to have quality of life for these studies as well.

Q: Why did A1c increase by the end of study?

Dr. Ryden: It's quite frequent that if you follow people with diabetes for a long time HbA1c increases due to the progression of the disease.

Q: Can you provide any comments on the Latin population?

Dr. Ryden: It was a small population, but in principle, the results went in the same direction and were of similar magnitude.

Q: What about this drug in African Americans?

Dr. Ryden: Since they made up a very small proportion of the patients this is a question that is difficult to give a firm reply to

Q: Regarding CANVAS and DECLARE, some may claim that these ongoing trials should be stopped in view of the placebo arm.

Dr. Kaul: I hope that DSMBs (safety committees) of ongoing cardiovascular outcomes trials don't take any decision in haste. We need to allow other studies to be completed to replicate the mortality benefit and rule out a potentially concerning stroke hazard. Diabetes drugs have a very checkered history when it comes to cardiovascular outcomes. We have seen a large treatment effect which is unexpected and unprecedented. There's the concern of the stroke signal. If we were to stop those trials, we would lose the opportunity to reliably assess the stroke signal. Dapagliflozin CVOT will accrue nearly twice the number of events thereby providing ample opportunity to refute or confirm the stroke signal seen in EMPA REG OUTCOME trial. Many patients and physicians will consider a disabling stroke as perhaps a worse outcome than death. A drug or class of drugs that reduces mortality but increases disabling stroke would be a wash in my opinion. I hope that they will not do that. CETP inhibitor, torcetrapib, had a highly significant 58% increase in cardiovascular mortality in the pivotal trial. Did the IRBs and DCMs recommend trials evaluating other drugs in the class be stopped? No. I would say it is imperative that we allow those studies to continue to replicate the mortality benefit and clarify the stroke signal.

Dr. Leiter: It will also depend on what happens to guidelines. If our standard of care changes, one may have to look at the studies and ask for consent from patients again. There will be a lot of conference calls over the next few weeks.

Dr. Ryden: These are very important questions for DSMBs but also for the trial physicians and the patients. They will read about the results in newspapers and start to wonder if they should have the drug rather than be in a study in which they may get placebo. Ongoing studies will be disturbed if the participants want to be on an active drug and leave the study. Studies addressing other than the present population should proceed. An example is a large trial of dapagliflozin in which a lot of the participants have a high risk for cardioavscular risk but no established cardiovascular disease. We need to know if SGLT2 inhibition works in these patients as well as in the just studied population

Symposium: Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS)

UPDATE ON TECOS SAFETY DATA

Robert Josse, MD (St. Michael's Hospital, University of Toronto, Canada)

Dr. Robert Josse presented an update on TECOS safety data, suggesting a possible class effect with increased risk for acute pancreatitis with DPP-4 inhibitors. As we learned at ADA, TECOS had an imbalance in acute pancreatitis with 23 vs. 12 cases (p=0.065) not in favor of sitagliptin. Dr. Josse presented a deeper analysis into the data, showing that severe or fatal pancreatitis occurred rarely, with four severe cases and 19 mild/non-severe cases. The median number of days from randomization to pancreatitis was 517 for the sitagliptin group vs. 528 for placebo. Regarding etiology, ten were of unknown etiology while two were alcohol-related, eight were biliary-related, and four were related to a prior pancreatitis history. Notably, Dr. Josse presented a meta-analysis of the three DPP-4 inhibitor CVOTs (SAVOR, EXAMINE, TECOS), which suggested a statistically significant increased risk of acute pancreatitis with an overall hazard ratio of 1.58 (p=0.033). However, he stressed to attendees the need to interpret these results with caution, noting that the trials had differences in follow-up duration and enrolled patient populations as well as variation in the adjudication procedures. As for pancreatic cancer (9 vs. 14 cases in favor of sitagliptin), Dr. Josse showed that a meta-analysis of SAVOR and TECOS (EXAMINE was not included as no cases were reported) suggested no difference in the risk of pancreatic cancer, despite the fact that the rates were numerically lower with the DPP-4 inhibitor group in both trials (HR=0.54; p=0.066). With the acute pancreatitis risk, we would suspect that these numerical imbalances in favor of DPP-4 inhibitor therapy are likely just due to chance, especially with the low number of cases. Yet increasingly, it appears that acute pancreatitis risk may be a class effect, although so far, we have heard most speakers playing the safety signal down. For example, Dr. Josse emphasized that it may not be a major clinical risk, noting that further post-marketing surveillance will help to determine the clinical relevance despite the meta-analysis' findings; Dr. John Buse (UNC, Chapel Hill, NC) similarly suggested at ADA that such a risk would be rare and acceptable within the class' otherwise strong safety profile. While in the aftermath of EMPA-REG, this information on pancreatitis risk is not the most compelling in terms of CVOT findings, we believe that it could still be somewhat useful for providers when individualizing second-line therapies for patients with a history of pancreatitis (although the evidence is likely not sufficient to drastically change current guidelines quite yet).

Corporate Symposium: Getting to the Heart of Type 2 Diabetes (Sponsored by Lilly/BI)

THE BROKEN HEARTED - CV RISK AND T2D MANAGEMENT

Kausik Ray, MD (Imperial College London, UK), Naveed Sattar, MD (University of Glasgow, UK), and Nikolaus Marx, MD (University Hospital Aachen, Germany)

Lilly/BI's corporate symposium tantalized the audience with frequent references to the big reveal of the EMPA-REG OUTCOME full results later in the week. Upon entering the packed auditorium, attendees were immediately greeted by a huge screen flashing a continuous loop of the words "SGLT-2," "CVOT," and "CVD," interspersed with EKG-style heartbeats and set to upbeat music. If that display had not already put attendees in the frame of mind to be thinking about the EMPA-REG OUTCOME trial, every seat in the room offered an invitation to the Lilly/BI-sponsored symposium on EMPA-REG OUTCOME immediately following the results presentation (really!). As a reminder, Lilly/BI released topline results from the trial last month stating only that Jardiance (empagliflozin) demonstrated cardiovascular risk reduction vs. placebo. Lilly and BI are definitely building up big interest up the full results - we certainly hope they live up to the publicity, though we believe even a fairly subtle effect, which may well be the result, would still be a big deal given the number of reduced deaths this would still indicate.

- **In his presentation during the symposium, Dr. Naveed Sattar (University of Glasgow, UK) asserted that the diabetes field needs more CVOTs moving forward because they are the only way to understand drugs' full effect on cardiovascular risk.** In the case of SGLT-2 inhibitors, he pointed out that the class is known to decrease blood pressure and weight (good in terms of cardiovascular risk), but it also raises LDL cholesterol (for unclear reasons but

potentially a concern). During the ensuing panel discussion, fellow presenter Dr. Kausik Ray (Imperial College, London, UK) echoed this point, stating that superiority (rather than non-inferiority) trials require investigators to be absolutely sure there are no off-target harmful effects first. We agree that outcomes trials certainly provide invaluable information about products' safety and efficacy but believe that the current FDA paradigm has important limitations that may prevent the trials from demonstrating the most clinically useful information (see below for more).

- **During the panel discussion, Dr. Ray and Dr. Sattar speculated on the potential drivers of the positive EMPA-REG OUTCOME results.** Dr. Ray was clear that he expects the blood pressure-lowering effect of SGLT-2 inhibitors to be the main driver of reduced cardiovascular risk, while Dr. Sattar suggested that it might be a composite effect of lower blood pressure, weight, and glucose.

PANEL DISCUSSION

Kausik Ray, MD (Imperial College London, UK), Naveed Sattar, MD (University of Glasgow, UK), and Nikolaus Marx, MD (University Hospital Aachen, Germany)

Q: Should future CVOTs demonstrate superiority rather non-inferiority?

Dr. Nikolaus Marx: From a cardiologist's point of view: of course, we'd love to see that and lots of cardiologists can't understand why these aren't being performed. But it's important to remember what is required by regulatory bodies. In future I hope to see superiority trials.

Dr. Kausik Ray: It really depends on what it is you want to do. One way to look at this is in terms of on-target benefits and on-target harm. Lower glucose has a cardiovascular benefit. If you change glucose levels, you might get a benefit, but it will take 25 years. On-target harm are things related to hypo. With any new class, we're worried about the off-target effects, like heart failure. If you're absolutely sure there are no off-target effects, then you can go straight to superiority trials. That's the big question, is it safe?

Dr. Naveed Sattar: Glucose and microvascular risk go hand in hand. Glycemic control is used to prevent microvascular complications. If a diabetes drug can also decrease macrovascular risk, that's an added bonus. That'd be fantastic. But the key issue is if it can do it without other safety issues and long term CVOTs help find that out.

Q: As a professor of public health, what are the most important messages we should be putting across?

Dr. Ray: Probably preventing diabetes in first place. Once you've got it, its progression is inevitable. Education is important, starting particularly in childhood - we're seeing anthropometric measures that are abnormal in the first decade of life.

Dr. Sattar: I think Dr. Ray is completely correct. The big public health battle is to reduce the number of excess calories in the environment. In addition, picking out people with diabetes early or at high risk to instigate lifestyle changes helps. If I can recognize somebody at high risk and I can encourage and help that individual make small sustainable lifestyle changes to delay diabetes for 5, 10 years, that's significant.

Dr. Marx: I have one simple sentence: don't forget about blood pressure and lipids.

Q: CVOTs vary considerably in length. Is there likely to be any difference in short-term vs long-term trials?

Dr. Marx: It depends on the intervention. If you look at statin trials, short-term trials already reduce risk. It's important to see the design of the trial. If the primary objective is non-inferiority, short-term may be appropriate.

Q: Are the effects of SGLT-2 inhibitors on blood pressure and weight reduction likely to account for superiority in CVOT?

Dr. Ray: From data I showed you, we've seen such consistent data on blood pressure and lipids that for me, the blood pressure-lowering effect, even if it's only 5 mmHg, is going to translate to a reduction in CV events.

With regards to weight loss and CV risk, we have not really seen major trials that show this relationship. For me, the blood pressure effect is really going to be what's driving it.

Dr. Sattar: When they report full results, I suggest looking to see if they're going to show data by baseline blood pressure - that's going to potentially informative. I think benefits could be mix of glucose, weight, and blood pressure benefits. But let's see. There may be a surprise in there.

Corporate Symposium: Evolving Perspective in Treating Diabetes and Obesity (Sponsored by Novo Nordisk)

CARDIOVASCULAR OUTCOMES TRIALS IN DIABETES: WHAT HAVE WE LEARNED AND WHERE ARE WE HEADING?

Marc Pfeffer, MD, PhD (Brigham and Women's Hospital, Boston, MA)

Dr. Marc Pfeffer stressed the importance of evaluating hard clinical outcomes rather than relying on surrogate markers like A1c to judge the effects of diabetes treatments. He joked that he did not intend to "pick on A1c," offering a long list of promising hypotheses in cardiology based on epidemiological studies with surrogate endpoints that were later disproven in outcomes trials. However, he did offer some criticism of existing CVOTs for diabetes drugs, particularly the fact that they do not include heart failure as a primary endpoint. This is a sentiment we have heard repeatedly over the past few years, and we suspect that at the very least there will be more efforts to prospectively collect detailed data on heart failure in future trials given the surprises (negative in SAVOR and positive in EMPA-REG OUTCOME) in trials thus far. Dr. Pfeffer closed by urging attendees to treat the whole patient by addressing multiple CV risk factors rather than putting on blinders and focusing only on A1c - another sentiment that is becoming increasingly common.

MECHANISMS IN CARDIOVASCULAR EFFECTS OF GLP-1

Mansoor Husain, MD (UHN Research, Toronto, Ontario, Canada)

Dr. Mansoor Husain explored some of the current research behind mechanisms of GLP-1's effects on the cardiovascular system. He began his presentation by illustrating that obesity is very interconnected with not only type 2 diabetes, but also hypertension, dyslipidemia, atherosclerosis, CAD, and more. However, a significant amount of data on GLP-1 agonists have shown that this drug class can improve survival post-myocardial infarction, can protect isolated hearts and cardiomyocytes, limit hypertension, and bring about other cardiovascular benefits. Delving into the mechanisms, Dr. Husain demonstrated through knock-out rat data that cardiac GLP-1 receptors are likely not required for post-myocardial infarction benefits, while other data suggests that hypertension is reversed through a GLP-1 receptor-dependent mechanism. In addition, GLP-1 agonists have been shown to induce diuresis and natriuresis, increasing atrial natriuretic peptide (ANP) levels in obese individuals with type 2 diabetes. With the recent positive EMPA-REG results, we would not be surprised to see even greater mechanistic research of diabetes drugs in cardiovascular outcomes in the near future.

Corporate Symposium: Lessons Learned from the TECOS CV Safety Trial and the Evolving Role DPP-4 Inhibitors in the Treatment of Patients with Type 2 Diabetes (Sponsored by MSD)

LESSONS LEARNED FROM THE TECOS CV SAFETY TRIAL: THE ROLE OF SITAGLIPTIN IN THE TREATMENT OF CARDIOVASCULAR PATIENTS WITH TYPE 2 DIABETES

Rury Holman, FMedSci (University of Oxford, UK)

Dr. Rury Holman reviewed the results from TECOS (CVOT for Merck's Januvia [sitagliptin]) presented at ADA and alluded to several limitations of existing CVOTs during Q&A following his talk. Dr. Holman said it would be a "very long time" before anyone can expect clinical data on the neuro-, cardio-, and nephroprotective effects of sitagliptin or other DPP-4 inhibitors. He believes a truly informative study would have to incorporate the glucose-lowering effects of the drug, and it would be difficult to do this ethically as a placebo-controlled trial given the known relationship between glucose control and microvascular

complications. He argued that even uncovering any protective glucose-independent effects would require a much longer trial than most companies would be willing to undertake - this is where we believe funding from non-industry sources can play a very useful role since once these agents are generic, it would of course be very useful to understand the true benefit. Given these concerns, he suggested that a head-to-head comparative outcomes study with agents from different classes are the most likely to reveal the true long-term benefits and harms of new drugs. We completely agree and see this as one of the ways in which more flexible FDA policy could enable more informative trials.

PANEL DISCUSSION

Dr. Michael Nauck (Diabeteszentrum Bad Lauterberg, Germany): You showed data showing that higher A1c equals higher heart failure risk. On the other hand, higher A1c should mean more glucosuria and osmotic diuresis, perhaps not enough to compensate, but does it matter?

Dr. Michel Komajda (Université Pierre et Marie Curie, Paris, France): I don't think so. At a high A1c you usually have alteration of vascular function and vessel changes, usually an increase in stiffness. It's a multifactorial issue and I don't think that point could explain a contradiction to the overall finding.

Q: Other DPP-4 inhibitors are approved for advanced impaired renal function. There's no clear data on sitagliptin having adverse effects in that population. Why wouldn't you use sitagliptin for this population?

Dr. Nauck: There's no doubt that sitagliptin can be used safely in renal impairment. You have to reduce the dose to keep exposure in the range we see in patients with no reduction in function. It's pretty obvious from these trials that sitagliptin doesn't worsen renal function in patients with a baseline reduction in GFR. And there's no obvious provocation of side effects that you wouldn't see in another population.

Q: Which DPP-4 inhibitors are safe in patients with diabetes and preexisting cardiovascular disease?

Dr. Nauck: Saxagliptin and sitagliptin have a neutral effect on macrovascular events. The only difference is an increased heart failure risk with saxagliptin that was not observed with sitagliptin. There was a mild increase in risk with alogliptin. All of these were patients with a chronic condition or all with multiple risk factors in SAVOR.

Q: Small percentages of patients didn't receive statins. Was that at the time of enrollment or at the end of the trial? Are you planning to do a post-hoc analysis of this subset?

Dr. Rury Holman (University of Oxford, UK): We have shown no difference in the primary outcome by statin therapy. We haven't pulled them out to see what happens longitudinally. The reasons they're not taking statins relates to adverse effects. It's not a randomized comparison.

Q: In heart failure patients, although you don't have a definition of ejection fraction, if the ejection fraction is below 40 can sitagliptin be indicated? Or is there still doubt?

Dr. Holman: For the study as a whole there was no imbalance and a tight confidence interval. It was a consistent result by whatever subgroup. You're correct that ejection fraction measurements were not collected. Some may have it in their records, but there wasn't a consistent proactive collection. I can't make a statement about it. We have seen complete consistency of the results however we slice the data.

Dr. Komajda: In the subset with previous heart failure, which was more than 2,000 patients, it is likely many had a low ejection fraction, and there was no harmful effect compared to placebo in recurrent heart failure events or cardiovascular mortality.

Q: Is there anything interesting in the BNP data?

Dr. Holman: That was not collected prospectively, but there is a plan for biomarkers that were collected to be measured. Whatever the level of prior heart failure, it doesn't influence the results. It's of interest to cardiologists but I don't expect it to be a differential. It's an analysis we plan to do but it's after the event.

Dr. Nauck: There are two roles of BNP: one is as a marker of worsening heart failure and it's also a substrate for DPP-4, but the action should not alter its biological activity, correct?

Dr. Carolyn Deacon (University of Copenhagen, Denmark): I don't think it alters its biological activity, but early reports say it might influence the half-life, so indirectly it might.

Dr. Komajda: When SAVOR was presented in the cardiology community there were lots of questions because we believed high BNP was beneficial. Giving a DPP-4 inhibitor reduces the catabolism of BNP, so it should increase it. There's no real plausible biological explanation why saxagliptin should be associated with increased heart failure risk, unlike what was observed with the TZDs, for instance, which we know induce sodium retention. It remains a question mark that will be addressed in future studies.

Q: The saxagliptin study showed an increase in heart failure. They stopped saxagliptin when they showed development of heart failure, so what happened then? Did it improve or was it the same?

Dr. Holman: We don't have that information. The study hasn't published that. But the study was double-blinded, so no one knew which drug they were on. It wasn't an expected adverse event, so they wouldn't necessarily have stopped study drug.

Q: Do we know what happens to cardiac performance in animals receiving either sitagliptin or others in the category?

Dr. Komajda: There's generally a favorable effect on cardiac function and the vasculature, which raised a lot of questions regarding the accuracy of the methods. At the moment we can say from preclinical studies that the consensus is that the effects are beneficial.

Q: What about vildagliptin in heart failure?

Dr. Komajda: That arises from the VIVID trial in patients with previous heart failure. It was a proof-of-concept study, not an outcomes study. They looked at cardiac dimensions 52 weeks after randomization and there was significant cardiac dilation, no real change in ejection fraction, and no increase in heart failure hospitalization. I don't know. At this point I do not recommend vildagliptin in a patient with overt heart failure or a previous history.

Dr. Nauck: It's a logical consequence that if you have diversity and there are some compounds that don't raise any question in that population, you should use those.

Q: How long should we expect to get results in humans to check the neuro-, cardio-, and nephroprotective effects of DPP-4 inhibitors?

Dr. Holman: A very long time. You would have to design trials that allow sitagliptin to be tested with a glucose differential. That's a problem because you have to treat glucose to reduce microvascular risk. It would be hard to have a glucose difference trial of any magnitude for a long time. So we look for non-glucose-related effects and we are reading between the lines that these are small differences, and I'm not sure a trial of the length of time it takes to see complications emerge is likely to be undertaken. I'd be interested to know if a company is contemplating that.

Dr. Nauck: Often I hear in discussions that these are disappointing results from a safety study, but it's a proven thing that as long as agents lower glucose, they will reduce microvascular complications. I would like to see proof from studies that show this rather than just assuming.

Dr. Holman: We need to manage glucose control by doing head-to-head comparisons between agents from different classes and truly seeing if there is long-term benefit or harm.

Dr. Komajda: It's a pity that the companies stopped the pioglitazone vs. rosiglitazone comparison. That kind of study would be helpful with DPP-4 inhibitors.

Dr. Holman: It's quite clear that in TECOS there was no signal. The question is whether the SAVOR signal is real. This was not an expected result, and we don't have a biologically plausible mechanism. We may have

stumbled on a problem. There's a degree of uncertainty that's not explained. There's clear data for which agent has no apparent effect, but we have a concern raised that has not yet been refuted.

Dr. Nauck: I'm a clinician prescribing glucose-lowering agents. With this information, it's difficult to justify ignoring it and prescribing a drug in someone with preexisting heart failure that has produced such results. If this is by error, how long will it take us to know better? We have to do even more trials, maybe head-to-head, and we will learn years from now, but we have to behave and prescribe drugs in the meantime. I'm characterizing my justification for prescription behavior based on published evidence.

Dr. Holman: We don't know for certain but clearly in the meantime we act on the data that's available.

Q: Have any studies shown a benefit of sitagliptin on neuropathy?

Dr. Holman: I'm not aware of any long-term studies, maybe some short-term ones.

Dr. Nauck: I believe there's promising animal data showing specific effects in certain models.

Q: Is there a role for DPP-4 inhibitors in type 1 diabetes?

Dr. Nauck: There was an observation from type 2 diabetes where in some trials a DPP-4 inhibitor used with insulin led to a reduction in A1c and reduced hypoglycemic episodes, there was some interest and a hypothesis put forward that it increased alpha cell sensitivity to changes in glucose. If glucose is high, it will suppress glucagon; if it's low it will increase glucagon. There's a little bit of evidence. It's a good idea to be tested but we don't have trial results.

Q: What happened to blood pressure in TECOS?

Dr. Holman: It was not changed at all.

Corporate Symposium: Different Patients, Different Needs - Towards an Integrated Care Approach to Diabetes (Sponsored by Sanofi)

GETTING TO THE HEART OF THE MATTER: UNDERSTANDING CV RISK IN DIABETES

Lars Rydén, MD, PhD (Karolinska Institute, Stockholm, Sweden)

Dr. Lars Rydén offered a thoughtful take on the limitations of CVOTs after reviewing the current evidence on the relationship between diabetes and cardiovascular disease. He pointed to several commonly cited shortcomings (short duration, disproportionately high-risk populations, glycemic equipoise design) and mentioned others that have attracted less discussion, such as a lack of attention to postprandial glucose and use of primary endpoints that do not include clinically relevant events like peripheral arterial disease, heart failure, and stable angina. He also cautioned that the promising findings from UKPDS have limited applicability to the modern type 2 diabetes patient population because so few patients were on blood pressure- and lipid-lowering drugs - he said the heavy use of such medications is likely one of the main reasons why it is so difficult for current trials to demonstrate superiority (we wonder if it's more a matter of just short timing). While the tone of Dr. Rydén's critique was not as strident as some of the commentary we heard recently at ESC, the implication seemed to be that the information gained from these trials may not be worth the enormous investment of patient time and financial resources. As he aptly noted, the design of current trials is driven by commercial and regulatory factors rather than academic research goals - yeah, that's pretty depressing given the potential impact on public health. We hope the FDA will feel compelled in the coming years to engage in a discussion about how the 2008 Guidance can be modified to encourage more cost-effective studies. We also hope that government, industry, academia, and private foundations can work together to develop creative ways to better answer the most important clinical questions about diabetes drugs and cardiovascular risk, such as through more robust large-scale databases or comparative effectiveness studies.

-- by Melissa An, Adam Brown, Helen Gao, Varun Iyengar, Emily Regier, and Kelly Close