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'Heart Failure Is Killing Your Diabetes Patients,' Experts Warn at EASD

Shelley Wood | Sep 26, 2013

BARCELONA, SPAIN — Cardiologists speaking here at the **European Association for the Study of Diabetes (EASD) 2013 Meeting** are urging diabetologists to sit up and take notice: heart failure is killing their patients and is not getting the attention it deserves.

Not only is heart failure one of the most lethal—if not *the* most lethal—complications of diabetes, its role in diabetes is being routinely overlooked by physicians, by journals publishing diabetes research, and perhaps worst of all, by regulators tasked with telling companies what's important for trials of new diabetes drugs.

Heart Failure in the Hot Seat

Their pleas come at a time when heart failure has vaulted once again onto the radar of physicians studying and treating diabetes, this time after a signal of increased heart failure was seen in the **SAVOR TIMI 53** trial. The results were presented at the recent **European Society of Cardiology (ESC) 2013 Congress** meeting and published simultaneously in the *New England Journal of Medicine*.

As reported by **heart*wire*** , patients randomized to the dipeptidyl peptidase-4 (DPP-4) inhibitor **saxagliptin** had a 27% increased risk of hospitalizations for HF as compared with placebo-treated patients. **EXAMINE** , a second cardiovascular-outcomes study of another DPP-4 inhibitor, **alogliptin**, also presented and published during the ESC meeting, did not include heart failure as a prespecified end point. A post hoc analysis presented for the first time here today indicated that HF hospitalizations were numerically higher in the alogliptin group than in the placebo-treated group, but the difference was not statistically significant.

Just how a clinical trial could travel from conception to publication without including heart failure as a stand-alone end point, given the lethal nature of this complication in diabetic patients, was a key talking point in an EASD session devoted to heart failure and diabetes.

"Not only do diabetologists, along with cardiologists, need to take heart failure seriously in patients with diabetes, but the regulators do as well," **Dr John J McMurray** (University of Glasgow, Scotland) urged the audience. "We need to make heart failure a much more prominent component of our clinical trials, and we must not see major journals publishing major CV-outcomes trials in diabetes and not even mentioning one of the most important — if not *the* most important — cardiovascular complication of diabetes, which is heart failure."

Heart Failure, Mortality, and Diabetes

For his presentation, McMurray reviewed the largest cardiovascular-outcome trials that included a predefined subset of diabetic patients, as well as the major diabetes trials that included cardiovascular outcomes. Only seven of 12 major CV-outcomes trials actually reported heart failure as an outcome, and worse still, of the 24 major diabetes-outcome trials, only 10 reported heart-failure outcomes.

In slide after slide, McMurray showed data from clinical trials that, for years, were household names for cardiologists

and endocrinologists alike, among them **VALUE** , **LIFE** , **RENAAL** , **HOPE** , **LOOK Ahead** , **ADVANCE** , and **ACCORD** . In all of them, he pointed out, the likelihood of developing or being hospitalized for heart failure among people with diabetes was as high as and in many cases higher than the risk for MI and universally higher than the risk for stroke or CV death.

"The story gets even more interesting when you look at patients who develop diabetic nephropathy," McMurray continued, showing a comparison of HF hospitalizations in diabetic patients in LIFE and RENAAL. Both of those trials evaluated **losartan** (vs placebo or **atenolol**), and both excluded patients with heart failure at baseline. The key point, however, was that regardless of treatment assignment, rates of HF hospitalizations were two to three times higher among patients with diabetic nephropathy than in diabetics with no nephropathy. Similarly, in the RENAAL, **IDNT** , and **ALTITUDE** trials, the most common CV outcome in patients with both diabetes and nephropathy was heart failure, which, again, was sometimes twice as common as MI.

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"You might be saying to yourselves, well, that's all very well, so heart failure is quite common: big deal, so what," McMurray chided the audience. "What I would like to show you is that heart failure is actually the most deadly of the cardiovascular complications."

Looking again at data from LIFE and RENAAL, McMurray showed that deaths over the several years of follow-up were at least twice as common in diabetic patients with heart failure than in diabetic patients without heart failure. In ALTITUDE, a more contemporary trial, deaths were markedly higher among patients who required HF hospitalizations than they were for patients hospitalized for death, stroke, or end-stage renal disease.

"And this doesn't speak to disability," McMurray added, noting that there is a wealth of evidence showing that HF "is a much more disabling CV disorder than MI and even stroke."

McMurray said he often hears from colleagues focused on diabetes who refer to heart failure as "just a bit of ankle swelling" or "a bit of fluid retention."

"I hope with the data I've showed you . . . that you [no longer] think that's the case."

History Repeating Itself?

Heart failure first emerged as an issue in the early glitazone trials but was ultimately eclipsed by concerns over MI, a possibility that made headlines worldwide in the now-infamous Nissen/Wolski **rosiglitazone** meta-analysis. Asked why MI concerns had held sway over HF risk, McMurray quipped: You'll have to ask **Steve Nissen** that question. He was focused on a signal of what he thought was MI, and sometimes when you focus on one thing, you don't see the bigger picture."

The rosiglitazone saga resulted in new **FDA** requirements for CV-outcomes trials with new diabetes drugs; SAVOR TIMI 53 and EXAMINE were the first two studies designed with these new criteria at their core.

Regrettably, said McMurray, the FDA opted not to include heart failure as one of the end points required by companies designing CV-outcome trials, opting instead for major adverse cardiac events, typically a combination of MI, stroke, and CV death.

"The FDA guidance says you can also consider unstable angina and revascularizations and does, as a throw-away

comment, say 'possibly look at other CV outcomes.' But that guidance clearly misses the elephant in the room, which is heart failure. I can hardly believe that it [instead] mentions things like coronary revascularization, which is a relatively soft, practice-driven end point and not one that reflects the development of CV disease."

The ESC guidance for trialists is slightly better, he continued. While still focused on "the same atherosclerosis-driven end points, it at least does mention that HF should be considered."

An alarming outgrowth of the FDA's current advice to companies, however, is that of 16 cardiovascular-outcomes trials for diabetes drugs either in development or already under way—enrolling almost 150 000 patients in total—not a single one of them will report heart failure as part of the primary outcome, McMurray noted.

Given the heart-failure signal recently seen in with the newer DPP-4 inhibitors, McMurray says he has grave concerns about what this might mean once many more patients are exposed to the drugs. "Unless something is very different in this trial [SAVOR-TIMI 53], this will be a very deadly event," he warns.

Diabetes Drug Safety in HF Patients

Dr Barrie (Miles) Fisher (Glasgow Royal Infirmary, Scotland), another speaker in today's special session, tackled the question of what diabetes therapies are actually safe, from a heart-failure standpoint, in treating dysglycemia.

"I'm afraid I haven't got that much definitive to say," Fisher lamented. Reviewing the scant evidence, Fisher concluded that **metformin** is "probably" safe; sulfonylureas, "we're not sure"; glitazones, "no"; DPP-4 inhibitors, "possibly not, but we need more data"; and for the glucagonlike peptide-1 (GLP-1) receptor agonists, "we just don't know."

Acknowledging that the heart-failure signal in SAVOR-TIMI 53 has been a major talking point at this meeting, alongside the numeric increase in HF events now reported for EXAMINE, Fisher predicts that other drugs in this class will face new scrutiny.

Is this an effect with one drug or is it a class effect, and is it only in certain groups of patients with HF, or will it become a clinical problem?

He pointed to **VIVIDD** , a study of another agent in this class, **vildagliptin**, which showed no differences in left ventricular ejection fraction out to 52 weeks. There was, however, a statistically significant difference in LV end-diastolic and LV end-systolic volume between the placebo- and vildagliptin-treated patients.

A change in volume "is not a good thing if you have heart failure. So this might start to hint at mechanisms."

As well, Fisher continued, DPP-4 plays a role in the degradation of a range of peptides. "I think we have to ask ourselves, could the increase in hospitalizations for HF with saxagliptin be explained by the accumulation of one or more of these peptides, or even a peptide that we haven't yet characterized? And that leads us to further questions: is this an effect with one drug or is it a class effect, and is it only in certain groups of patients with HF, or will it become a clinical problem? As further CV-outcomes studies come out for this class, we will be looking very closely at their results."

Turning to the GLP-1 agonists, Fisher noted that these agents have a known risk of volume depletion in "vulnerable patients," particularly the elderly. "In heart failure, you want to get fluid volumes down, but not excessively. So it might be that these drugs give some additional benefit in HF patients, but it might be that they give some additional harm. It's really too soon to say."

For Cardiologists: Test for Diabetes, Watch for HF

In the third presentation of the dedicated session, **Dr Darren McGuire** (University of Texas Southwestern Medical School, Dallas), a cardiologist, reviewed evidence-based medications that are proven to reduce the risk of heart failure both in diabetic and nondiabetic patients. Efficacy is similar in both groups, he noted, but given the higher risks associated with heart failure in diabetic patients, the benefits of controlling risk factors in these patients would likely be amplified.

A key issue, noted McGuire, is the large proportion of patients with unrecognized diabetes, even those in the care of cardiologists. Citing four cardiovascular-disease cohorts, McGuire pointed out that "new diabetes" diagnoses at the time of a particular CV procedure ranged from 15% to more than 30%. Combined with previously diagnosed disease, diabetic patients made up half of the patients across the four cohorts.

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As a side note, McGuire also offered himself up as a prime example of someone who has failed to fully appreciate the impact of heart failure in diabetic subjects.

"I've been interested in diabetes for about 15 years now as an exclusive focus both clinically and as an investigator, but I haven't paid much attention to heart failure until I got invited to this talk," he admitted. "So I've had the . . . myopic focus on atherosclerosis for far too long."

To **heart*wire*** , McMurray reiterated his call to all doctors treating patients with diabetes to watch out for heart failure and treat it aggressively and to consider what diabetes drugs they use in this group.

"It's not just fluid retention; these people die," McMurray stressed. "When you talk to endocrinologists, that's exactly the kind of comment you hear. We need to get across that if you develop HF it doesn't matter if it is on rosiglitazone, it's not just that you've retained some fluid, no matter what has happened to you to get there, you are on a completely different prognostic trajectory, where you are going to do very badly indeed."

Fisher disclosed advisory payments from AstraZeneca/Bristol-Myers Squibb, Boehringer Ingelheim, Eli Lilly, GlaxoSmithKline, Janssen, MSD, Novartis, Novo Nordisk, Sanofi, and Takeda. McGuire disclosed consulting for Genentech, F Hoffman LaRoche, Takeda, Janssen, Sanofi, Boehringer Ingelheim, Merck, and Bristol-Myers Squibb and research support from Genentech, F Hoffman LaRoche, Takeda, Boehringer Ingelheim, Merck, Daiichi Sankyo, Orexigen Therapeutics, Eli Lilly, Bristol-Myers Squibb, AstraZeneca, and GlaxoSmithKline. McMurray has previously disclosed consulting for Bristol-Myers Squibb, Guidant Europe, and Cardiokinetix.

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