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Heart failure event definitions in drug trials in patients with type 2 diabetes

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In 2008, the US Food and Drug Administration (FDA) issued guidance for industry mandating that drug companies show that new drugs for the treatment of type 2 diabetes do not increase the risk of cardiovascular disease;¹ however, this guidance focuses on cardiovascular death, myocardial infarction, and stroke, but not on heart failure.² Type 2 diabetes is independently associated with an increased risk of admission to hospital with heart failure.³ Furthermore, heart failure caused by antidiabetic drugs has reemerged as a concern because of the increased risk of admission to hospital with heart failure associated with the DPP-4 inhibitor saxagliptin.^{4–6} Udell and colleagues⁷ showed that glucose-lowering strategies might increase the risk of heart failure.⁷ The American College of Cardiology and American Heart Association⁸ define a heart failure event as worsening signs and symptoms of heart failure, signifying failure of the primary therapeutic management strategy, and resulting in escalation of therapy as an outpatient or requiring hospital admission.⁸ However, specific definitions of heart failure events used in clinical trials of antidiabetic drugs have not been systematically assessed. In view of recent clinical trial results, we propose an update to existing criteria for heart failure events. This Comment is based on discussions among scientists, clinical trialists, industry sponsors, and regulatory representatives, which took place at the 11th Global Cardiovascular Clinical Trialists Forum (Washington DC, USA; Dec 5–7, 2014).

We identified 15 completed antidiabetic drug trials (appendix). Five (33%) of these trials did not provide heart failure event definitions. The UKPDS and ACCORD trials used non-specific definitions of heart failure events. More recent trials (EXAMINE, SAVOR-TIMI, TECOS, AleCardio, and EMPA-REG OUTCOME) provided more specific heart failure criteria. Only the PROactive trial^{9,10} provided data for heart failure not requiring admission

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to hospital (appendix). None of the trials required a specific biomarker (brain natriuretic peptide [BNP] or N-terminal pro-BNP [NT-pro-BNP]) cut-off to define heart failure events. Heart failure definitions in clinical trials have clearly been changing over time, with older trials using less precise definitions and newer trials using more specific definitions—probably because of the increasing recognition of heart failure events in patients with type 2 diabetes.

Although the relative risks for heart failure within a trial are likely to be unbiased, the absolute estimates of heart failure risk will differ between trials because of differences in heart failure event definitions. This situation makes assessing heart failure results between different trials challenging. In the PROactive trial,^{9,10} heart failure events were reported as adverse events rather than as part of the primary composite endpoint, and were therefore not adjudicated. Although subsequent adjudication¹⁰ of events did not significantly change the results, because regional practices and the threshold for admitting patients with heart failure to hospital vary, masked adjudication with standardised definitions of heart failure events is crucial to allow comparisons between studies. Worsening heart failure symptoms in patients who do not require admission to hospital are not routinely assessed but might be increased by antidiabetic drugs—eg, in the PROactive trial,⁹ worsening heart failure not requiring hospital admission was increased with pioglitazone. Because outpatient management of worsening heart failure is resource-intensive, reporting this risk as a secondary outcome might affect use of specific antidiabetic drugs by health-care professionals.

The challenges in identifying heart failure events arise predominantly from the clinical criteria used to define heart failure (appendix). Signs and symptoms that suggest heart failure to one physician might be perceived as a respiratory illness by another. Dyspnoea in patients presenting to the emergency department might have multifactorial causes, and escalation of diuretic therapy is often done empirically and concurrent with other treatments such as antibiotics, steroids, and bronchodilators. In clinical trials in which heart failure endpoints are defined by admission to hospital, it could be reasonable to mandate objective evidence of heart failure, such as biomarker elevation.⁸ Although event definition guidelines do not mandate biomarkers use,⁸ clinical guidelines have advocated measurement of BNP or NT-pro-BNP to support clinical judgment for diagnosis of acutely decompensated heart failure.¹¹ Previous analyses have shown substantial variation in heart failure event definitions.¹² To increase the specificity of adjudicating heart failure events, use of biomarkers (such as BNP) in combination with imaging (such as echocardiography) is recommended.¹² Although adjudication might not be absolutely necessary, objective measures of heart failure such as biomarkers might increase confidence in event adjudication. For patients experiencing worsening heart failure not requiring admission to hospital or requiring management in outpatient clinics, features such as weight gain, radiographic or biomarker evidence,¹¹ and escalation of oral diuretic therapy with resultant improvement of symptoms and subsequent weight loss might be used to define a heart failure event.

We propose a modification of current criteria⁸ to define a heart failure event (panel). In current recommendations, heart failure events are defined by the presence of at least one heart failure symptom, at least two physical examination findings, or one physical

examination finding and at least one laboratory criterion, and initiation or intensification of heart failure treatment.⁸ Laboratory criteria are biomarker evidence, radiographic evidence of pulmonary congestion, non-invasive diagnostic evidence of heart failure (eg, by echocardiography or MRI), or invasive haemodynamics. We recommend more prominent use of biomarker and radiographic or hemodynamic evidence criteria (panel). There are challenges to such an approach since local biomarker assays have substantial variation in measurements and cut-off s. Unlike for troponin, no universally accepted cut-off definition exists for biomarkers of heart failure. Furthermore, investigators designing a clinical trial would need to specify when to collect such biomarker data and whether a central laboratory would be needed to ensure standardisation. However, such a strategy would enable heart failure events to be more objectively defined (either through adjudication or from case report forms) and would enable events from different geographical sites to be more consistently defined. For worsening heart failure in outpatients, an event can be defined by signs, symptoms, and intensification criteria, since biomarkers and radiographic evidence are not always available.

In view of the heterogeneity of definitions for heart failure events in clinical trials in patients with diabetes, standardised international definitions are needed to ensure consistency between diabetic cardiovascular outcome trials. Investigation of worsening heart failure symptoms in patients who do not require admission to hospital should also be considered. Although biomarkers such as BNP or NT-pro-BNP might not be absolutely essential, we recommend more prominent inclusion in heart failure definitions to identify patients with true exacerbation of heart failure.

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Panel**Proposed criteria for defining heart failure**

A heart failure event for patients treated in the emergency room or admitted to a hospital and treated as an inpatient should be defined by meeting at least one criterion from each subheading below (biomarker evidence, radiographic or haemodynamic evidence, heart failure symptoms, and intensification of treatment) and at least two for heart failure signs. For outpatient worsening of heart failure, because biomarker and radiographic or haemodynamic evidence might not be obtainable, an event can be defined by meeting one criterion from each of the heart failure symptoms, signs, and intensification of treatment subheadings.

Biomarker evidence

At least one of the following:

- Brain natriuretic peptide (BNP; eg, 100 ng/L)
- N-terminal pro-BNP (eg, 300 ng/L)

Radiographic or haemodynamic evidence

At least one of the following:

- Non-invasive diagnostic evidence of heart failure (eg, echocardiographic, cardiac MRI)
- Radiographic evidence of pulmonary congestion
- Invasive cardiac catheterisation suggesting evidence of heart failure (eg, pulmonary capillary wedge pressure [or left ventricular end-diastolic pressure] >18 mm Hg, right arterial pressure [or central venous pressure] >12 mm Hg, or cardiac index < 2.2 L/min per m²)

Heart failure symptoms

At least one of the following:

- Dyspnoea
- Decreased exercise tolerance
- Fatigue
- Worsened end-organ perfusion
- Other symptoms of volume overload (eg, swelling of legs, increase in abdominal girth, etc)

Heart failure signs

At least one of the following:

- Peripheral oedema
- Increasing abdominal distension or ascites

- Pulmonary rales or crackles, or crepitation
- Increased jugular venous pressure, hepatojugular reflux, or both
- Third heart sound or gallop
- Clinically significant rapid weight gain related to fluid accumulation (>1·4–1·8 kg in 3–4 days)

Intensification of treatment

At least one of the following:

- Augmentation of oral diuretic therapy
- Intravenous diuretic or intravenous vasoactive therapy
- Mechanical or surgical intervention (eg, mechanical circulatory support or mechanical fluid removal)