Heart failure: a cardiovascular outcome in diabetes that can no longer be ignored

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In patients with type 1 or type 2 diabetes, glycaemic exposure assessed as HbA1c correlates strongly with risk of future microvascular and macrovascular complications. Improved glucose control substantially reduces the risk of microvascular complications and, with extended follow-up, modestly reduces the risk of atherosclerotic events. The lowering of HbA1c concentrations by newly developed glucose-lowering drugs (alone or when added to other glucose-lowering drugs) has been used, until recently, as a surrogate measure of their potential to lower cardiovascular risk. This assumption is no longer acceptable, and now demonstration of cardiovascular safety has been mandated by regulatory authorities. A major concern, however, is the universal absence in any large-scale trials of new glucose-lowering drugs of hospital admission for heart failure as a prespecified component of the primary composite cardiovascular outcomes. This omission is important because hospital admission for heart failure is a common and prognostically important cardiovascular complication of diabetes. Moreover, it is the one cardiovascular outcome for which the risk has been shown unequivocally to be increased by some glucose-lowering therapies. As such, we believe that heart failure should be systematically evaluated in cardiovascular outcome trials of all new glucose-lowering drugs.

Introduction

Regulatory approval of a new therapeutic drug is based on the achievement of a cumulative level of clinical trial evidence showing that the intervention is both effective and safe (as far as is possible to establish safety within the limits of early discovery). The definitions of effective and safe are highly dependent on the disease condition and standards of international regulatory agencies. In patients with type 1 or type 2 diabetes, improved glycaemic control substantially reduces the risk of microvascular complications, and modestly reduces the risk of cardiovascular events with extended follow-up.1–4 Lowering of HbA1c concentration by glucose-lowering drugs has been used, until recently, as a surrogate measure of their potential to reduce cardiovascular risk.1–3 Registration trials generally included stable patients with a raised HbA1c, and had follow-up measured in weeks or months.1–3 When sufficient evidence of glucose-lowering efficacy had been accumulated for regulatory submission, tabulations of serious and less serious adverse events were also provided, usually with a focus on treatment-related outcomes such as symptomatic hypoglycaemia. The prevailing assumption was that lowering of glucose would, in the long run, lead to beneficial patient outcomes, defined as fewer microvascular and hopefully macrovascular events.1–3 Many cardiovascular and diabetes researchers, however, strongly advocated the importance of explicit measurement of macrovascular events during the evaluation of new drugs for diabetes. After a high-profile meta-analysis suggesting that a particular drug that was effective at lowering glucose might also increase the risk of myocardial infarction, important and constructive changes in the regulatory process for assessment of new drugs to treat diabetes were finally announced.4

The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) both issued new guidance aimed at assuring more statistically robust demonstration of cardiovascular safety for new treatments for diabetes before they can enter the market.10,11 In effect, sponsors must show that their drug will not result in an unacceptable increase in cardiovascular risk.5–10 This guidance has resulted in a huge increase in the number of randomised trials in patients with diabetes, done mainly to evaluate safety, with so-called major adverse cardiovascular events (MACE) as the primary outcome. MACE generally has been defined as the composite of cardiovascular death, myocardial infarction, or stroke, although the guidance states that other relevant cardiovascular events such as hospital admission for acute coronary syndrome, urgent revascularisation procedures, and other endpoints can be considered. On a positive note, the new guidance from the FDA and EMA has led to substantial increases in exposure of patients with cardiovascular disease to new compounds before they are approved.

At present roughly 150 000 patients with either known cardiovascular disease or a high burden of cardiovascular risk factors are being followed up in randomised trials of new glucose-lowering drugs. This international effort will undoubtedly improve definition of the cardiovascular safety and efficacy profile of these drugs, and provide these data at an earlier marketing stage than hitherto. A major concern, however, is the universal absence in any of these trials of hospital admission for heart failure as a prespecified component of their primary composite cardiovascular outcomes. In our opinion, hospital admission for heart failure is one of the most common and prognostically important cardiovascular complications of diabetes, and the one cardiovascular outcome for which the risk has been shown unequivocally to be increased by certain glucose-lowering therapies. Thus, we believe that heart failure should be systematically evaluated in cardiovascular outcome trials of new glucose-lowering drugs, either as a component of the primary composite outcome or as a prespecified secondary endpoint.
What is heart failure?
Heart failure is the term used to describe a common clinical syndrome arising as a consequence of impaired cardiac pump function. The most typical symptoms are breathlessness and fatigue and the most common sign is peripheral oedema. The syndrome of heart failure can arise as a result of almost any abnormality of the structure, mechanical function, or electrical activity of the heart. Many of the typical clinical symptoms and signs of heart failure do not arise directly as a result of the cardiac abnormality, but rather from secondary dysfunction of other organs and tissues—eg, the kidneys, bone marrow, and muscles. These secondary consequences of pump failure are myriad and are not explained solely by reduced perfusion; it is generally believed that other systemic processes such as neurohumoral activation and inflammation are involved.

In developed countries, left ventricular dysfunction is the commonest underlying problem and is caused, mainly, by myocardial infarction (leading to systolic ventricular dysfunction—ie, failure of normal contraction and emptying of the heart), hypertension (causing systolic dysfunction, diastolic dysfunction—ie, failure of normal relaxation and filling of the heart), or, often, both infarction and hypertension. Patients with cardiac dysfunction can remain asymptomatic for months, years, or even decades. However, once symptomatic heart failure has developed the syndrome is characterised by progressive worsening of the patient’s symptoms, of cardiac function, and of the function of other tissues (eg, skeletal muscle, bone marrow) and organs (eg, the kidneys). Quality of life is greatly diminished, hospital
admission for exacerbations are common, and mortality is high.12,13 In clinical trials, unplanned hospital admission for heart failure is typically defined as requiring all of presentation with typical symptoms, the presence of typical signs, and treatment with intravenous therapy.14

### Diabetes as a causal factor for heart failure?

Whether diabetes should be considered a causal factor or a comorbidity in heart failure is unclear.15,16 Its potential role in causation of systolic and diastolic dysfunction is uncertain. Individuals with diabetes have a higher prevalence of heart failure than those without diabetes. Diabetes accelerates the development of coronary atherosclerosis and is often associated with hypertension. Whether it directly causes a specific cardiomyopathy is, however, uncertain. Diabetes is also associated with an increased risk of developing heart failure in patients with other causes—eg, acute myocardial infarction. Diabetes is believed to promote the development of myocardial fibrosis and diastolic dysfunction. Diabetes is also associated with increased autonomic dysfunction and worsened renal and endothelial function, impaired gas exchange, as well as worsened functional status and a poor prognosis.15,16

### Frequency of heart failure in diabetes

Observational data illustrate the frequent occurrence of heart failure compared with other cardiovascular events. For example, Juhaeri and colleagues17 examined the incidence of hospital admission for myocardial infarction, stroke, and heart failure during a 6-year period among 65619 patients with type 2 diabetes treated with insulin, in a large US claims database. The rate of myocardial infarction was 97/10000 (1134 cases), stroke 151/10000 (1746 cases), and heart failure 243/10000 (2786 cases).

Despite such epidemiological findings, a review of 19 trials in patients with type 2 diabetes (or a mix of type 1 and type 2 diabetes) showed that 12 did not report heart failure as an outcome; another review reached similar conclusions and two more recent trials also failed to report heart failure.18–21 Inspection of reports of the diabetic subgroup among patients enrolled in 12 trials of chronic arterial disease or hypertension revealed similar findings.26–28 Tables 1 and 2 summarise drug-therapy trials that did report heart failure as an outcome.26–28 Comparison across trials is difficult because of the differing entry criteria for each and because of varying definition of the endpoints. Some trials included so-called silent myocardial infarction with clinically recognised events and some trials included episodes of heart failure not leading to hospital admission in the definition of non-fatal heart failure. Despite these difficulties, it is clear that in the recent large-scale trials of glucose-lowering therapies, heart failure occurred at a frequency similar to that of stroke

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### Table 2: Cardiovascular events in diabetic subgroups of patients in clinical trials of patients with chronic arterial disease, hypertension, or acute MI

<table>
<thead>
<tr>
<th>Participants</th>
<th>Diabetic subgroup from trials in patients with chronic arterial disease, hypertension, or both</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HOPE* (MICRO-HOPE; ≥55 years)</td>
</tr>
<tr>
<td>Age ≥55 years with CVD, or ≥1 cardiovascular risk factor</td>
<td>Age &gt;18 years; CHD</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Exclusion criteria</th>
<th>Diabetic subgroup from trials in patients with acute myocardial infarction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nephropathy, HF, or LVEF &lt;40%</td>
<td>SAVE* (n=496)</td>
</tr>
<tr>
<td>HF or LVEF &lt;40%</td>
<td>VALIANT* (n=3400)</td>
</tr>
</tbody>
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| Median/mean follow-up (years) | 4.5 | 4.3 | 4.7 | 4.2 | 2.5 | 3.5 | 1.0* |

| Outcomes | Cardiovascular deaths, n (%) | 284 (8%) | 107 (7%) | 99 (8%) | 2861 (5%) | 136 (2%) | 133 (27%) | 548 (16%) |
|          | All MI, n (%) | 414 (12%) | 134 (9%) | 91 (8%) | 299 (6%) | 168 (2%) | 94 (19%) | 308 (10%) |
|          | Fatal MI | – | – | – | – | – | – | – |
|          | Non-fatal MI | – | – | – | – | – | – | – |
|          | All stroke | 184 (5%) | 43 (3%) | 116 (10%) | 234 (4%) | 134 (2%) | – | 97 (3%) |
|          | Fatal stroke | – | – | – | – | – | – | – |
|          | Non-fatal stroke | – | – | – | – | – | – | – |
|          | All HF | 434 (12%) | 39 (3%) | – | 412 (8%) | 141 (2%) | 156 (31%) | 664 (21%) |
|          | Fatal HF | – | – | – | – | – | – | – |
|          | Non-fatal HF | – | – | 87 (7%) | – | – | – | – |

Empty cells denote outcomes not reported for that trial. MI=myocardial infarction. CVD=coronary artery disease. CHD=coronary heart disease. LVH=left ventricular hypertrophy. LVEF=left ventricular ejection fraction. HF=heart failure. ACE=angiotensin-converting enzyme. LV=left ventricular. *1 year follow-up was used for this analysis. (Cardiac death. 

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and myocardial infarction. It should be noted that this outcome was despite most trials excluding patients with more than mildly symptomatic heart failure (or heart failure altogether) and the exclusion by many trials of elderly patients, who are particularly likely to develop heart failure. In the 5145 low-risk participants in the Look AHEAD (Action for Health in Diabetes) trial, the rate of development of heart failure in the control group (0·42 per 100 patient-years) was greater than that of stroke (0·36) or cardiovascular death (0·22). The rate of myocardial infarction was 0·71 per 100 person-years. Only in the older UK Prospective Diabetes Study (UKPDS) was the risk of heart failure substantially less than that of myocardial infarction. Of the 3867 patients enrolled in UKPDS, 573 (15%) had a fatal or non-fatal myocardial infarction, 203 (5%) a stroke, and 116 (3%) developed heart failure over a median 10 years of follow-up. UKPDS, however, enrolled only patients with newly diagnosed diabetes and without known cardiovascular disease. Conversely, heart failure appears to be a more common complication of advanced diabetes, particularly when nephropathy develops (figure 1). Indeed, as shown in table 1, the occurrence of heart failure was actually more frequent than myocardial infarction in the Reduction in Endpoint with the Angiotensin Antagonist Losartan (RENAAL) and Irbesartan Diabetic Nephropathy Trial (IDNT). Not only was heart failure a common first cardiovascular event in these patients, but it recurred more frequently than other major cardiovascular outcomes. For example, in IDNT, among the 1715 patients randomly assigned to treatment groups, 225 (13%) had 336 episodes of heart failure compared with 117 (7%) patients (128 episodes) with myocardial infarction and 69 (4%) patients (76 episodes) with stroke. A similar observation was made in patients with diabetes without nephropathy in the Prospective Pioglitazone Clinical Trial in Macrovascular Events trial (PROACTIVE). In that trial, 144 placebo-treated patients (5%) had 157 non-fatal myocardial infarctions (including silent infarctions), 107 (4%) had 119 strokes, and 108 patients (4%) had 153 hospital admissions for heart failure (90 [3%] patients also had 117 episodes of heart failure not needing hospital admission). Most recently, among the 8561 patients in the Alikiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints (ALTITUDE), hospital admission for heart failure was a more frequent occurrence (424 patients) than either fatal or non-fatal myocardial infarction (289 patients) or stroke (269 patients).

Several trials of interventions in patients with chronic arterial disease or hypertension have reported cardiovascular outcomes separately in a diabetic subgroup. These reports also reveal that heart failure was at least as common as was myocardial infarction (and more common than stroke) in most studies (table 2, figure 2). The findings of clinical trials are consistent. For example, in DIABHYCAR, 638 (13%) of 4912 patients died during follow-up. Among patients not admitted to hospital for heart failure, 68 (36%) of 187 died an average of 12 (SD 11) months after their first admission. Development of heart failure in RENAAL (mean 3·4 years) and LIFE (mean 60 months) followed by a mortality rate of 32·7 per 100 person-years compared with 3·7 per 100 person-years in patients with diabetes who remained free of heart failure.

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failure subsequently died compared with eight (15%) of 52 patients surviving a first hospital admission for acute myocardial infarction (overall, 7% of patients in RECORD died). In other words, in RECORD, subsequent outcomes in patients admitted to hospital for heart failure were worse than for patients admitted with acute myocardial infarction.

Effects of diabetic therapy on incidence of heart failure

Regulatory agencies have stressed the importance of ensuring that new glucose-lowering drugs are safe or beneficial with respect to myocardial infarction or stroke. No glucose-lowering drug has, however, been shown clearly to cause either of these problems. Conversely, two such drugs (the thiazolidinediones pioglitazone and rosiglitazone) have each been shown to increase the risk of heart failure (table 3). The two major outcome trials with these drugs, RECORD and PROACTIVE, identified a substantial increase in risk of heart failure, although heart failure was not a prespecified, adjudicated endpoint in PROACTIVE. In PROACTIVE, 198 (8%) patients on placebo had 302 heart failure events compared with 281 (11%) patients (417 events) in the pioglitazone group (hazard ratio [HR] 1·41, 95% CI 1·10–1·80, p=0·007).

Figure 2: Cumulative risk of myocardial infarction and heart failure in VALUE overall (valsartan and amlodipine groups combined), according to diabetes status. Reproduced from Akses et al, with permission of Wolters Kluwer Health.

Figure 3: Mortality in patients with diabetes with and without heart failure in LIFE and RENAAL. Kaplan-Meier curves illustrating cumulative mortality rate in patients who did and did not develop heart failure during (A) the LIFE trial and (B) RENAAL. The heart failure:no heart failure hazard ratio for mortality was 5·98 (95% CI 3·90–9·17, p<0·0001) in LIFE and 3·99, 95% CI 3·02–5·25, p<0·0001) in RENAAL. Reproduced from Carr et al, with permission of Elsevier.
Retrospective adjudication of these events showed close concurrence with the investigator reports. In RECORD, 61 (3%) of 2220 rosiglitazone-treated patients had at least one admission to hospital for heart failure whereas 29 (1%) of 2227 patients in the placebo group had this outcome (HR 2.6, 95% CI 1.1–4.1, p=0.001).

Despite previous speculation that thiazolidinediones-induced heart failure does not carry the same prognostic importance as heart failure occurring in other patients, and might just reflect fluid retention caused by these drugs, recent evidence from RECORD suggests otherwise. In RECORD, the risk of hospital admission for heart failure was roughly doubled in the rosiglitazone group (table 3). Of the 61 rosiglitazone-treated cases of heart failure, the first event was fatal in four and 17 (30%) of the 57 surviving patients died during the remainder of the trial. In the control group, 29 patients had a first hospital admission for heart failure, none of which was fatal subsequently, and eight (28%) of these 29 patients died during follow-up (compared with 6.1% and 7.5% deaths overall in the rosiglitazone and control groups, respectively). The relative safety of pioglitazone compared with rosiglitazone is unlikely ever to be known after the premature termination of the Thiazolidinedione Intervention with vitamin D Evaluation (TIDE).

Recently, the dipeptidyl peptidase-4 (DPP-4) inhibitor saxagliptin has also been shown to increase the risk of hospital admission for heart failure, compared with placebo (3.5% vs 2.8%, p=0.007) in the Saxagliptin Assessment of Vascular Outcomes Recorded in patients with diabetes mellitus–Thrombolysis In Myocardial Infarction (SA VOR-TIMI) 53 trial in which 16,492 patients with type 2 diabetes and established cardiovascular disease, or risk factors for cardiovascular disease, were followed up for a median of 2.1 years. Whether this completely unexpected finding reflects the play of chance, is drug specific, a DPP-4 inhibitor class effect, or even an issue for other incretin-based therapies (eg, glucagon-like peptide-1 analogues) is unknown at this point, but once again emphasises the importance of heart failure as an outcome in diabetes. Not only was heart failure a much more frequent event than stroke, but also it was nearly as common as myocardial infarction and was the only major cardiovascular event (including death) affected by the study drug. The findings of SA VOR-TIMI 53 are clearly at odds with the observation that heart failure is characterised by high DPP-4 activity and that reducing this activity with DPP-4 inhibitors has beneficial effects in experimental models of heart failure.

Another trial of a DPP-4 inhibitor, the EXamination of CArdiovascular OutcoMes: AlogliptIN vs. Standard of CarE in Patients with Type 2 Diabetes Mellitus and Acute Coronary Syndrome trial (EXAMINE) has also reported heart
failure as part of an exploratory composite outcome. Although not published in full at the time of writing, the EXAMINE investigators have reported a greater number of hospital admissions for heart failure in the alogliptin group compared with the placebo group, although this difference was not statistically significant.29

The effect of other antidiabetic treatments on the occurrence of heart failure is unknown, with the exception of insulin glargine, which was tested in the Outcome Reduction with an Initial Glargine Intervention trial (ORIGIN) in patients with impaired fasting glucose, impaired glucose tolerance, or early diabetes, and cardiovascular disease or risk factors (table 1).29 The rate of hospital admission for heart failure was 0.85 per 100 patient-years in the insulin group compared with 0.95 per 100 patient-years in the control group.29 It should be noted, however, that the 88% of patients in ORIGIN with diabetes had their disease for a mean duration of 5.4 years, 6% had a new diagnosis, and 23% were receiving no pharmacological therapy before randomisation. Patients with diabetes of longer duration are at greater risk of heart failure and might be at greater risk of drug-induced heart failure.

Why might treatments for diabetes increase the risk of heart failure?

Because little attention has been paid to heart failure as an outcome in patients with diabetes, it is not surprising that even less is known about the possible mechanisms underlying the effects of thiazolidinediones and possibly DPP-4 inhibitors on this cardiovascular outcome. Although thiazolidinediones were recognised to cause fluid retention, possibly through a distal tubular action, this process cannot be the whole explanation for the findings of the RECORD and PROACTIVE trials because, in many cases, patients developed pulmonary oedema necessitating emergency admission to hospital. Not only that, but such events were associated with a dismal subsequent prognosis.30 One possibility is that fluid retention unMASKS heart failure in susceptible individuals with undiagnosed underlying left ventricular dysfunction, a common problem in patients with diabetes.30 Thiazolidinediones are not known to have a direct toxic or negative inotropic action.

The explanation for the findings of SAVOR-TIMI 53 (assuming they are not just the play of chance) is even less clear. At the time of writing, no further information was available about the nature of the heart failure identified or the outcomes in patients who developed heart failure in this trial. DPP-4 has many substrates and its inhibition might affect many biological pathways including, potentially, those as diverse as enzymes affecting cardiac collagen turnover and the sodium/hydrogen exchanger isoform 3 in the renal proximal tubule.31–33 A direct toxic or negative inotropic action of DPP-4 inhibitors has not been proposed to date, and most studies have suggested the opposite effect.34,35 Alternatively, a detrimental myocardial energetic consequence of reduced blood and tissue glucose and insulin might provide a unifying explanation for the findings with both thiazolidinediones and DPP-4 inhibitors.36 This unsatisfactory state of affairs needs urgent attention and rectification with both improved studies on myocardial function in patients with concomitant diabetes and heart failure, as well as on the cardiac effects of new pharmacological treatments for diabetes. Fortunately, at least some of the ongoing trials in patients with type 2 diabetes are collecting information about possible cases of heart failure, either as part of an expanded secondary cardiovascular composite outcome37 or as a stand-alone endpoint (see also NCT01147250, NCT01144338).38

Limitations

Our focus has been clinical trials and these have mainly reported cases of heart failure leading to hospital admission. Although patients admitted to hospital have the worst prognosis, even heart failure that does not lead to admission is an ominous development. Our focus on patients admitted to hospital will also have underestimated the incidence of heart failure in patients with diabetes. Another potential limitation of our critique is that some might argue that composite outcomes should reflect the same disease process—eg, atherosclerosis or atherothrombosis—as reflected in the MACE outcome of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke used in almost all recent and ongoing trials of antidiabetes drugs. A counter argument is that composites might also reflect all major and common events that represent the burden of the disease in question to patients and society; heart failure is highly relevant from this perspective. For any composite outcome, interpretation is difficult when a treatment has divergent effects on individual components and this problem might be more likely with components that do not reflect the same disease process.

Search strategy and selection criteria

To examine heart failure occurring in trials in diabetes, electronic databases including PubMed, Embase, CINAHL, and the Cochrane Library were searched up to Dec 1, 2013. We restricted the search to randomised controlled trials done in among human adults (age ≥19 years) and published in English; there were no date restrictions. Our search of the Medline database was done through PubMed using the medical subject headings (MeSH) terms for heart failure: “Heart Failure” or “Cardiomyopathy, Dilated”, which include the following definitions: cardiac failure; myocardial failure; left sided heart failure; right sided heart failure; congestive heart failure; heart insufficiency; systolic heart failure; diastolic heart failure; cardiac oedema; paroxysmal dyspnoea; dilated cardiomyopathy; congestive cardiomyopathy; familial idiopathic cardiomyopathy. Diabetes was identified using MeSH terms “diabetes mellitus”, “type 2”, “haemoglobin A1c”, “glycosylated”, “glycated”, “glucose”, “cardiovascular disease”, and “heart failure” as well as the non-MeSH terms “glycaemic control”, “glucose control”, and “aggressive/intensive/tight”. Bibliographies of reviews, guidelines, and all publications identified by the search strategies were systematically reviewed. International experts and pharmaceutical firms were also consulted to identify uncompleted, unpublished, or overlooked studies.
Conclusions
Clearly, the occurrence of heart failure in patients with diabetes, although poorly reported in existing clinical trials, is frequent and is of ominous prognostic importance. Admission to hospital for heart failure should have equal status to myocardial infarction and stroke as an important cardiovascular outcome in studies of new diabetic therapies, and even added as a component to the primary composite cardiovascular outcome of trials to more fully capture the potential cardiovascular risks and benefits. It is notable that while the argument is made that the lack of a demonstrable beneficial effect of glucose-lowering drugs on atherothrombotic events reflects the short duration of contemporary clinical trials (with the hypothesis that a much longer and sustained reduction in glucose is necessary to decrease macrovascular events), the timeframe of these trials has been more than sufficient to detect an adverse effect on heart failure.1

Contributors
JJVMM wrote the first draft of the paper. All other authors critically reviewed and edited the content.

Declarations of interest
JJVMM reports that his employer, Glasgow University, has been paid for his time spent as a steering committee member, data safety monitoring board member, and endpoint committee member in diabetes trials by Bayer, GlaxoSmithKline, Lilly, Merck, Novartis, Sanofi-Aventis, and Oxford University. HCC reports consulting fees from Sanofi-Aventis, Novo Nordisk, Lilly, Bristol-Myers Squibb, Roche, AstraZeneca, Boehringer Ingelheim, and GlaxoSmithKline, lecture fees from Sanofi-Aventis and Bayer, and support for research or continuing education through his institution from Sanofi-Aventis, Lilly, Merck, Novo Nordisk, Boehringer Ingelheim, Bristol-Myers Squibb, Takeda, and AstraZeneca. RBH has received research funding from Bayer, BMS, and Merck and advisory board honoraria from Bayer, Eli Lilly, Merck, Novartis, and Novo Nordisk. MAP has received research grant support from Bayer, Celladon, Novartis, Sanofi Aventis; has acted as a consultant for Aastrom, Abbott Vascular, Amgen, Cerenis, Concert, Fibrogen, GlaxoSmithKline, Hamilton Health Sciences, Medtronic, Merck, Roche, Servier, Teva, and University of Oxford; and The Brigham and Women’s Hospital has patents for the use of inhibitors of the renin-angiotensin system in selected survivors of myocardial infarction with Novartis, for which he is a co-inventor, but his share of the licensing agreement is irrevocably transferred to charity.

References


