Time to move on from ‘time-to-first’: should all events be included in the analysis of clinical trials?

Stefan D. Anker¹,²* and John J.V. McMurray³

¹Applied Cachexia Research, Department of Cardiology, Charité, Campus Virchow-Klinikum, Augustenburger Platz 1, D-13353 Berlin, Germany; ²Centre for Clinical and Basic Research, IRCCS San Raffaele, Rome, Italy; and ³BHF Glasgow Cardiovascular Research Centre, University of Glasgow, Glasgow, UK

Online publish-ahead-of-print 27 August 2012

This editorial refers to ‘Effect of ivabradine on recurrent hospitalization for worsening heart failure in patients with chronic systolic heart failure: the SHIFT Study’³ by J.S. Borer et al., on page 2813

Not that long ago a diagnosis of heart failure was a death sentence. For example, a patient hospitalized with heart failure in the late 1980s had a median survival of <1.25 years after discharge. Those with reduced ejection fraction (HF-REF) died either from progressive pump failure or suddenly, mainly due to ventricular arrhythmias. This picture has been transformed in the past two decades. Angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, mineralocorticoid receptor antagonists, and devices (implanted cardioverter defibrillators and cardiac resynchronization therapy) have completely changed the prognosis for patients with HF-REF. Systolic heart failure has been converted from a relatively short-term and quickly fatal condition to a chronic disease characterized by recurrent non-fatal events (hospital admissions) and delayed death that is now nearly as often due to a non-cardiovascular as a cardiovascular cause.

Our design of clinical trials and choice of endpoints has to reflect this changing pattern of disease. All-cause mortality is no longer considered an appropriate or practical endpoint for clinical trials in heart failure. First, the mortality rate in heart failure has decreased so dramatically that trials using death as the primary outcome have become unfeasibly large. Secondly, as outlined above, non-cardiovascular deaths now account for a substantial proportion of deaths in heart failure. As they are unlikely to be reduced by a therapy for heart failure, their inclusion in a primary endpoint obscures the effect of treatment on the disease in question by adding ‘noise’. Thirdly, and most importantly, all-cause mortality does not fully reflect the current burden of disease, i.e. it neglects hospital admission.

Recognition of all of the above has led to the use of composite mortality–morbidity outcomes in more recent trials, initially all-cause mortality or heart failure hospitalization and, most recently, the more ‘disease-specific’ composite of cardiovascular death or heart failure hospitalization. However, there is still a problem with the standard approach to evaluating outcomes in clinical trials, which is based upon what is usually referred to as ‘time-to-first’ event analysis. In a trial using the composite of cardiovascular death or heart failure hospitalization, a patient has a ‘primary endpoint’ if he or she experiences cardiovascular death as the first of these two possible events or heart failure hospitalization. Clearly, a patient may experience cardiovascular death after heart failure hospitalization (indeed is more likely to do so because of hospitalization) and may also experience repeat heart failure hospitalization, but neither of these subsequent events count in the ‘time-to-first’ event analysis. As a result, ‘time-to-first’ event analyses of even a disease-specific mortality–morbidity composite do not fully reflect the true burden of HF-REF in a contemporary population (and this may be even more the case in patients with heart failure and preserved ejection fraction).

Indeed, ‘time-to-first’ event analyses ignore a vast amount of information on patient outcomes in a condition such as heart failure (Table 1). This can also be seen in the analysis of the Systolic Heart failure treatment with the I:\ inhibitor ivabradine Trial (SHIFT), where Borer and colleagues³ show that although 1186 patients had at least one heart failure hospitalization (which contributed to the ‘time-to-first’ event analysis, along with 544 cardiovascular deaths), 472 patients had two or more admissions and there were 2113 hospitalizations for heart failure and 940 cardiovascular deaths in total, i.e. 44% of all heart failure hospitalizations and 42% of cardiovascular deaths were ‘ignored’ in the ‘time-to-first’ event analysis. While the impact of death is obvious, the importance of heart failure hospitalization should not be underestimated. Such admissions are not only distressing for patients and their families, but they are also harbingers of accelerated disease progression (manifest by increased risk of re-admission and death) and the major driver of the economic burden of heart failure. Consequently, it is important to quantify the influence of treatment on these recurrent, non-fatal, events because the true benefit of treatment...
should be determined by its effect on all events (including repeat events) and not just first events.

Consider the theoretical (but probably unlikely) situation of two treatments with a similar effect on first events but where one was less effective at preventing repeat events; the second treatment would clearly be less valuable. Conversely, a similar or greater effect on repeat events (as on first events) would make a treatment more attractive. This can be seen with ivabradine in the analysis by Borer et al. Considering only first admissions, compared with placebo, ivabradine treatment prevented 47 patients per 1000 treated being admitted at least once for worsening heart failure. Taking account of repeat events, ivabradine prevented 93 hospital admissions for heart failure per 1000 patients treated.

Although the principle of accounting for recurrent events may be straightforward, how this should be done statistically is not. Recurrent events are not independent. One can only have a second hospitalization after having experienced a first, and one can only experience a third after a second, and so on (and must be alive to do so). In addition, recurrent hospitalizations tend to cluster in a subgroup of patients experiencing many more than the average number of hospitalizations during a given period of time. These and other considerations invalidate standard statistical techniques, which treat events as independent observations and assume proportionality of hazard. Statistical tests have been developed to attempt to mitigate these problems, including negative binomial regression (and the somewhat similar Poisson regression with adjustment for overdispersion), the Andersen–Gill method with robust standard errors, the method of Wei, Lin, and Weisdorf, and others. 2–5 Not all of these tests were specifically developed to deal with repeat event analyses, and some give results that are not easily interpretable. Indeed, the complexity of these tests is beyond the understanding of most clinicians, and the differences between and advantages and disadvantages of all the methods available are unclear to us.

One criticism of analysis of repeat events is that a small fraction of patients can contribute disproportionately to the overall burden of admissions. However, it is also true that if these individuals could be identified they would be an appropriate target for more intensive monitoring and treatment.

The competing risk of death must also be accounted for, first because any admission with worsening heart failure accentuates the risk of death, and secondly because dead patients can no longer be admitted. In SHIFT, the overall number of deaths was similar in both treatment groups and hence this issue was less of a problem than it may be in studies showing decreases or increases in death due to active therapy.

There are few trials in cardiovascular medicine that have reported analyses of this type, and only one recent trial in heart failure, CHAMPION, that used a recurrent events analysis as the primary endpoint. 6 We know of no treatment in cardiovascular medicine that has been approved on the basis of this type of analysis.

There are other approaches to taking account of the patients total experience of (or journey through) illness, such as days alive and out of hospital (also referred to as days of hospital-free survival), into which can also be factored quality of life. 7 This alternative approach is even less familiar to clinicians who are more used to the concept of a relative reduction in events as opposed to days of event-free survival. To date, experience in this new approach in cardiovascular medicine is limited (although these types of analyses are more commonly used in other disease areas). Trialists, statisticians, industry, and regulators interested in cardiovascular disease still have much to learn about it. The SHIFT analysis of recurrent events is a timely step in this collective learning process.

Conflict of interest: S.D.A. reports receiving fees for consulting from Amgen, Bosch Healthcare, Lonestar Heart, Vifor and Relypsa, and fees for speaking from Amgen, Servier, Novartis and Vifor.

References


<table>
<thead>
<tr>
<th>Trial</th>
<th>Time-to-first-event (CV death or HF hospitalization): CV death as % of primary outcome (n/n = N)</th>
<th>Recurrent events (all CV deaths and all HF hospitalizations): CV death as % of all events (n/n = N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHARM-Added</td>
<td>316/705 = 1021 (31.0%)</td>
<td>649/1443 = 2092 (31.0%)</td>
</tr>
<tr>
<td>CHARM-Alternative</td>
<td>237/503 = 740 (32.0%)</td>
<td>471/1053 = 1524 (30.9%)</td>
</tr>
<tr>
<td>EMPHASIS-HF</td>
<td>188/417 = 605 (31.1%)</td>
<td>332/702 = 1034 (32.1%)</td>
</tr>
<tr>
<td>SHIFT</td>
<td>544/1186 = 1730 (31.4%)</td>
<td>940/2113 = 3053 (30.7%)</td>
</tr>
<tr>
<td>l-PRESERVE</td>
<td>392/661 = 1053 (37.2%)</td>
<td>612/1176 = 1789 (34.3%)</td>
</tr>
<tr>
<td>CHARM-Preserved</td>
<td>190/509 = 699 (27.2%)</td>
<td>340/968 = 1308 (26.0%)</td>
</tr>
</tbody>
</table>

n/n, CV death/HF hospitalization; N, CV death or HF hospitalization (time-to-first event) or total number of CV deaths plus total number of HF hospitalizations (recurrent events). CV, cardiovascular; HF, heart failure.