

## The age of RCT's

### 3 Important Aspects of RCT's in Cardiovascular Pharmacotherapy with examples from Lipid and Diabetes Trials.

#### Review 1: Selection of endpoints for clinical trials

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## **Background**

Randomized clinical trials (RCTs) have revolutionized modern cardiovascular therapy. They are now the gold standard to prove efficacy of new treatment modalities with drugs, devices, surgery, and other interventions. Moreover, by allowing for the play of chance, RCTs also provide important information on safety and tolerability of a treatment. Furthermore, the randomization procedure eliminates both known and unknown confounders. This opens the opportunity to prove causality of an intervention for outcome.<sup>1</sup>

Trialists try to do their best to provide utmost quality of all aspects of RCTs. After completing a trial, we often hear that many lessons had to be learned from the respective trial and that the next trial should take this gain in knowledge into account.

With a series of three review articles, the authors aim to focus on critical methodological aspects of RCTs. This article focuses on endpoints and will be followed by a second article on rules to stop trials, and a third one will deal with subgroup analysis. According to the specificity of our Journal, we specially look at trials on cardiovascular drugs and will preferentially provide examples of metabolic interventions, e.g. by lipid lowering and hypoglycemic drugs.

## **The case for hard endpoints**

The cornerstone of RCTs is the recording of hard clinical endpoints instead of surrogates. At the time of the establishment of the protocol for a RCT, many interests have to be taken into account. A clinical researcher wants to provide innovation on treatment and to have an opportunity for high impact publications; and the sponsor wants to demonstrate progress by a new treatment and to open a new market. Thus, both sides want to end up with a positive trial. An important step is therefore to select the appropriate endpoints.

What is an appropriate endpoint? From a clinical standpoint it is the benefit for the patient, which includes survival without severe debilitating disease like stroke. In that respect, a

hierarchy of endpoints was proposed by J. Lubsen (adapted to Figure 1).<sup>2,3</sup> The major distinction is between hard and soft endpoints.<sup>4</sup> Some studies also consider costs. However, although important, this is not a medical target. After the disturbing results of Flosequinan, the need to include mortality as an endpoint in cardiovascular studies has become a requirement from the regulatory agencies (*see below*).<sup>5</sup> However, more recently, regulatory agencies have become more open to include benefits other than mortality in the approval of new drugs. Major, well-defined morbidity endpoints like myocardial infarction (MI) and stroke are examples. Furthermore, with the reduction of cardiovascular mortality because of the effective treatments proven in the past decades, also hospitalization for cardiac causes has become a relevant end-point.

### **Hierarchy of endpoints**

Efficacy endpoints must be clinically relevant and can be hierarchically divided into three groups. Group 1: all cause mortality, cardiovascular mortality, non-cardiovascular mortality; Group 2: morbidity i.e. MI, stroke, hospitalization for cardiac causes, and revascularization; and Group 3: surrogate endpoints, effects on quality of life, and posthoc endpoints (Figure 1).<sup>6</sup>

### **Mortality endpoints**

The hardest endpoint level is mortality. “Dead or alive” is a clear and easily recordable natural endpoint. It becomes more difficult to prove the cause of death. When considering cardiovascular endpoints, deaths from well-documented MI or stroke (with imaging proof) are highly trustable. Moreover, unwitnessed sudden death is also often due to MI or stroke; however, pulmonary embolism, primary ventricular fibrillation, aortic rupture are rarely proven or disproven to be the cause of death and nevertheless often figure under cardiovascular death.<sup>7</sup>

Beyond any doubt is all-cause mortality. It is the holy grail of endpoints reflecting a net benefit with regard to fatal events. Yet, it is clear that all-cause mortality by itself is a composite endpoint. Traditionally, mortality has been sub-categorized into cardiovascular versus non-cardiovascular. As a rule, e.g. in lipid interventions, cardiovascular but not non-cardiovascular mortality was reduced, but it was essential to demonstrate that the non-cardiovascular mortality was not increased as it may reflect fatal adverse effects (e.g. death from cancer). This “dogma” was recently broken by the ODYSSEY OUTCOMES trial,<sup>8</sup> where it was shown that also non-cardiovascular deaths were reduced in the intervention group in parallel with cardiovascular deaths.<sup>1</sup>

Although all-cause mortality should be the preferred mortality endpoint in cardiovascular studies, both all-cause death and cause-specific death must be assessed and reported. Cardiovascular death may represent an adequate endpoint providing that the therapeutic effect on all-cause mortality is at least neutral. In other words, some excess in non-cardiovascular mortality can be acceptable if the all-cause mortality is reduced. It is always of pivotal importance to define the mode of cardiac death and a central adjudication of the causes of death may be warranted.

### **Composite endpoints**

In RCTs of cardiovascular pharmacotherapy, primary endpoints include major adverse cardiovascular events (MACE, classically a 3-point MACE, i.e. the total of cardiovascular death, non-fatal stroke and non-fatal MI); hospitalization for cardiac causes is frequently added (e.g. in heart failure studies). Composite endpoints are commonly used in order to reduce the sample size or duration of the study, especially when a low event rate is expected. These endpoints are acceptable but must include mortality. The disadvantage of broader composite endpoints which include softer endpoints should be considered because softer endpoints may dilute the contrast between groups.<sup>9</sup>

Thus, a legitimate way towards a positive trial outcome is to test for composite endpoints, particularly if the segments considered are of the same cause like the atherosclerosis-related endpoints stroke, MI, and cardiovascular deaths.<sup>9</sup> Such an approach is particularly useful if the trial tests a more intensive versus a standard regimen, and not an intervention versus placebo. Survival studies using positive control drug(s) may be acceptable but should be limited to drugs that have consistently shown efficacy on survival, as it has been the case for statins in the past. Examples are PROVE-IT<sup>10</sup> and IMPROVE-IT.<sup>11</sup>

As to death, either all-cause mortality or cardiovascular mortality are useful as part of the composite endpoint. For the reasons outlined above, all-cause mortality appears preferable. The objective then is to increase survival without MI or stroke, an outcome that is well accepted in the broad public.

### **Non-Fatal endpoints**

Among non-fatal events, it is mandatory to distinguish between natural events (e.g. MI or stroke) and physician-driven events like revascularization procedures.<sup>12</sup> The former represent the natural progression of disease similarly to mortality and can be proven by ECG/troponins or imaging, respectively. The latter are open to judgement of the clinician for indication and therefore less objective. Revascularization should be regarded as a soft endpoint.

Nevertheless, the category of revascularization is often necessary e.g. in peripheral artery disease trials to end up with a significant result. If it is the only one, the outcome of the trial is debatable. If revascularization is embedded in hard endpoints like in FOURIER<sup>13</sup> it makes trials earlier positive. However, revascularization endpoints can also result in confusion, *see below*.

### **Myocardial infarction as an endpoint**

The definition of MI has changed importantly over the last decades. First, it was considered a myocardial necrosis that clinically was reflected as an event with acute chest pain, rise of creatine kinase, and typical ST elevation, an entity nowadays termed STEMI (ST elevation myocardial infarction). Next, it became clear that also myocardial necrosis without ST elevation but with other ECG changes exists, leading to the term NSTEMI (non ST elevation myocardial infarction). More recently, in recognition of the excellent sensitivity of new troponin assays - but perhaps deemphasizing specificity -, any event with elevated troponins in a clinically suggestive situation is classified as an MI. In this context, diagnosis of MI has become much more sensitive but also can represent considerably less myocardial damage, and ultimately be a softer endpoint. Given the evolving definition of MI, the adjudication of this endpoint in clinical studies is important.<sup>14</sup>

### **Unstable angina**

Among cardiovascular endpoints, a matter of debate is hospitalization due to unstable angina. For clinicians it is a common experience that chest pain patients often are admitted to hospital with the aim of not missing a severe condition. However, the diagnosis may be uncertain. In many trials, unstable angina emerged as a useless additional endpoint. Anyway, in the era of high-sensitivity troponins many formerly diagnosed cases of unstable angina nowadays will be NSTEMIs. In contrast, a very good example of thoroughly recording unstable angina as an endpoint is ODYSSEY OUTCOMES<sup>8</sup> where it was required to go along with typical history, ECG changes, and contemporary evidence of coronary obstruction. In summary, however, we take the position to judge unstable angina not as a reliable hard endpoint.<sup>15</sup>

### **A judgment of revascularization and unstable angina**

Taken together, the experience from modern cardiovascular trials rather is against including revascularizations or unstable angina into a composite endpoint because they do not add much clarity to the overall outcome and even may dilute the result. Such an experience followed the PROACTIVE trial<sup>16</sup> testing pioglitazone versus a comparator regimen. The primary composite endpoint included revascularization operations together with death, MI, and stroke and failed significance. In sharp contrast, the predefined secondary endpoint of death, MI, and stroke without revascularization was significantly positive. The simple failure to meet the primary

endpoint resulted in viewing the trial as not positive. This is an example how the ambitious selection of endpoints to force a trial into success may end up in the opposite. A further example how soft endpoints in composite may lose study success by dilution is TRACER ACS.<sup>17</sup> Therefore, for composite endpoints we would request to combine only hard endpoints like MI, stroke and death. We would discourage to impute also revascularization or unstable angina. Anyway, it should always be discernible what hard endpoints occurred in the study. There is traditional acceptance that a 3-point MACE (death, MI, or stroke) is a valid and meaningful composite endpoint.<sup>15</sup>

### **A new paradigm: Total events**

A very interesting innovation in endpoint acquisition is the total event paradigm. Up to very recently, endpoints were recorded as the time that passed from the onset of study to the first event. With Cox regression analysis, this time to first event was the one-or-nothing parameter to be compared between the treatment arms. In this way, an individual patient could only score once in the conduct of the study. However, if this patient had a second event, the latter did not count. This means that multiple events in the same patient are not counted which represents a loss in sensitivity to distinguish outcome between treatment arms. This lack is taken into account by the recently more often used approach of “total events”. Composite endpoints including recurrent events are now becoming increasingly used in cardiovascular trials and can serve as primary composite endpoint. Here, with different statistical methods one counts also two or more events in a given individual. This concept promises to detect differences better between treatment arms.<sup>18</sup>

Consistently, recurrent morbid events are becoming a popular and acceptable predefined endpoint in cardiovascular trials. Different methods for the analysis of recurrent event analysis have been proposed because they should be assessed with appropriate statistical methods. Usually hospitalizations for cardiac causes represent a frequent recurrent event to include in the analysis alongside the terminal event. Time-to-recurrent cardiovascular-related hospitalizations may therefore, be adjusted for correlated terminal cardiovascular (CV) events (all-cause death, fatal stroke, etc.). The analysis of recurrent events can be performed after study patients have been observed for an adequate follow-up or when an adequate number of adjudicated events have occurred (counting multiple events per subject).

For example, by counting total events, IMPROVE-IT<sup>11</sup> demonstrated superiority of the combination of ezetimibe 10 mg and simvastatin 40 mg daily versus simvastatin 40 mg alone, which was more pronounced in the recurrent events analysis than in the classical Cox regression approach. Similar results are reported from ODYSSEY OUTCOMES<sup>19</sup> and very recently from REDUCE-IT<sup>20</sup>. Thus, total events recording is a valuable way to prove benefit of

an innovation, particularly if a more intense intervention is compared to a standard one. The “total endpoint burden” is very important for the patient as well as for the health-care system. Because it is so logical to record total events, we cannot see any reason why it should not become a primary strategy in all RCTs. One disadvantage of the total events approach may be that a patient with multiple events is weighted higher than one with only a single event. Of course, no advantage is offered by the total events` analysis if the first event is a fatal one.

### **Surrogate markers**

By definition, surrogate parameters are not endpoints but rather risk factors (like LDL cholesterol or HbA1c) or imaging measures (like plaques in carotid ultrasound or coronary calcium in computerized tomography). In phase III outcome trials, surrogates cannot be accepted as endpoints. In contrast, information from phase II trials can be very useful for the conception of a RCT. For example, the intense reduction of LDL cholesterol seen with PCSK9 antibodies in phase II trials had an important impact on the planning of RCT duration, dosage and on other considerations in the RCTs. Weintraub, Lüscher and Pocock in an excellent review<sup>21</sup> came to the conclusion that with surrogates there is some peril and that not all surrogates are equally bad. To become valid, a surrogate should provide a strong association with outcome measures, consistent evidence from different trials, a significant correlation with endpoints in each trial, and a close link to endpoints. Moreover, the type of population of the particular RCT should be taken into account<sup>21</sup>.

An important aspect of the quality of a surrogate is causality. A positive example is LDL cholesterol where we have a strong impression of causality from epidemiology, mendelian randomization and intervention studies<sup>22</sup>. In contrast, glycemic interventions in diabetes mellitus - which is a strong risk factor for cardiovascular disease – failed to predict outcome measures. Even more surprising, RCT`s demonstrated that outcome can be significantly improved by SGLT2 inhibitors<sup>23–25</sup> and some GLP1 receptor agonists without lowering blood glucose importantly more than in the comparator arms.<sup>26–28</sup> Although hyperglycemia is the established cause of microangiopathy, such a connection of glucose with macroangiopathy is less clear; this can explain the observed results above. Probably in future high-dimensional biological data, including data from gene expression could be used as new useful surrogate markers.

### **Adjudication of endpoints**

A further discussion relates to adjudication of endpoints. Adjudication by a blinded external panel indicates some arbitrary element in the way to arrive at uniformity in diagnosis of a clinical entity that counts as an event. The issue is particularly relevant, for example, in the era of troponin or biomarker elevations as criteria for infarction, where precise interpretations,

especially in timing with regard to peri-interventional findings may vary between sites. Adjudication is a tedious and expensive process. In most trials, adjudication confirms most of the investigator-reported events. The COMPASS trial piloted a semi-automated system which reduced the need for manual adjudication by some 40%.<sup>29</sup>

### **Net benefit**

Whenever an intervention has an intrinsic risk for harm like antithrombotic therapy, the concept of net benefit is an important endpoint. Net benefit is e.g. reduction of MI or stroke minus the increase of bleed. The latter then usually is semi-quantitatively assessed as major or minor and specified for regions, like gastrointestinal versus intracranial bleed in the trials of NOAC`s.<sup>30</sup> The severity and clinical importance of the good event versus the severity and clinical importance of the bad event can importantly influence this net benefit.

### **Loss of follow-up**

Loss to follow-up is a meaningful number in outcome evaluation. The lower it is, the better. However, whether the loss favors an overestimation or an underestimation of results is difficult to assess.<sup>31</sup>

### **Predefined versus post-hoc endpoints.**

The gold standard in RCTs must be a predefined primary endpoint, regardless if it is a single or a composite one. Consistently, also if a secondary endpoint is chosen, it has to be predefined. In a strict evidence-based sense, no post-hoc endpoints are acceptable. However, reality can require post-hoc analyses if they appear beneficial for medical patient-related reasons. One example is that CANVAS, a trial with the SGLT2 inhibitor canagliflozin, reported increased amputation rates in the *verum* group.<sup>24</sup> Therefore post-hoc analysis of this endpoint appeared mandatory in the other two trials of SGLT2 inhibitors, EMPAREG OUTCOME<sup>23</sup> and DECLARE<sup>25</sup>, in order to find the truth. No evidence for this problem arose which underlined the predefined favorable safety outcome in those studies. In positive contrast, the findings of reduced hospitalization rates for heart failure under SGLT2 inhibitors prompted a post-hoc look into ejection fraction findings in those studies.

### **Regulatory aspects of approval**

Clinical trials have shown that LDL-lowering therapy with HMG-CoA reductase inhibitors reduces the risk for coronary heart disease (CHD) and that the relationship between LDL-C levels and CHD risk is consistent over a broad range of LDL levels. Furthermore, there is not a clear cut off to define "normo-cholesterolemia" and "hyper-cholesterolemia". Indeed, epidemiologic data indicate that for a given level of cholesterol, the cardiovascular risk



increases according to the associated risk factors. Other lipid disorders such as hypertriglyceridemia may be present in patients with elevated cholesterol levels (“mixed hyperlipidemia”) or may be isolated or associated with low high density lipoprotein cholesterol (HDL-C) (atherogenic dyslipidaemia, high non-HDL-C).<sup>32</sup>

Type 2 diabetes is a cardiovascular equivalent and it is a complex disorder which involves various degrees of decreased beta-cell function and peripheral insulin resistance. Glucose control in patients with type 2 diabetes mellitus deteriorates progressively over time, and, on average requires a new intervention with glucose-lowering agents every 3-4 years in order to obtain/retain good control. However, there are conflicting data on whether glucose control assessed by HbA1c is an adequate marker of efficacy. Indeed, in the past decades studies aimed at tight glucose control have failed to demonstrate benefit. Some glucose lowering drugs are associated with increased risk of cardiovascular events and for this reason the regulatory agencies (EMA, FDA) require mortality/morbidity studies to demonstrate the safety of new glucose lowering agents. These studies can be conducted as post-marketing commitment in Europe. More recently, however, newer glucose lowering drugs have shown to reduce cardiovascular events and mortality in diabetic patients.<sup>33</sup> This opens the question on future drug development of glucose lowering drugs.

For the approval of new drugs for the treatment of lipid disorders and diabetes mellitus, demonstration of efficacy on lipid levels and glucose control respectively are required. These data are usually required from short-term studies and longer-term studies are required to demonstrate safety. Furthermore, the demonstration of an effect on clinical outcomes is of pivotal importance for drugs acting on lipid metabolism and will be also central in the development of glucose lowering drugs.

A relative reduction in LDL-C level is an adequate primary efficacy endpoint in patients with primary hypercholesterolemia, provided that claims in the label are restricted to a lipid lowering effect. An isolated effect on TG or HDL-cholesterol is not an adequate proof of efficacy for new lipid-modifying agent. The effect should be contextualised in conjunction with the effect on non-HDL cholesterol. The preferred primary endpoint to show a beneficial effect of cardiovascular end points should be a composite of major cardiovascular events (CV or all-cause death, non-fatal myocardial infarction and non-fatal stroke). These events should be adjudicated by a blinded, independent committee. If cardiovascular instead of all-cause mortality is used as primary endpoint, the effect of the new treatment on non-cardiovascular mortality should also be evaluated.<sup>34,35</sup> The inclusion of other events, such as transient ischemic attack, silent MI, unstable angina pectoris or therapeutic interventions (need for PCI (Percutaneous Coronary

Intervention)) can be used to increase statistical efficiency and therefore, reduce the sample size and/or trial duration.

In the past, cardiovascular safety had not been systematically assessed in the context of the clinical development of glucose lowering agents. After the withdrawal from the EU market of rosiglitazone, both EMA and FDA have requested that the development programme of glucose-lowering medications should provide sufficient information supporting the lack of a drug-induced excess cardiovascular risk. The emphasis of the safety studies should be on major cardiovascular events, CV death, non-fatal myocardial infarction and stroke, but hospitalisation for unstable angina could also be included in a composite endpoint if the main objective is to exclude a macrovascular safety signal. Events such as revascularization and/or worsening of heart failure should also be evaluated as appropriate according to the drug profile.

### **Insights from RCTs in peripheral artery disease into endpoints.**

In studies also including peripheral artery disease patients, additional endpoints arising from the lower extremities are important. Major adverse limb events (MALE) refer acute complications in the limb: and are defined as acute limb ischemia, major amputation, or urgent revascularization<sup>13</sup>. Among these, revascularizations are the most frequent entity, including both surgery and transluminal interventions. Similar to what was summarized above on coronary revascularizations, these procedures are not considered hard endpoints. In contrast, major or minor amputations are harder endpoints. FOURIER<sup>36</sup> showed for the first time that a reduction in MALE is brought about by robust LDL-C lowering. Future RCTs of lipid and diabetes therapy should consider MALE as important endpoints.

### **Endpoints selection in observational studies**

All the rules outlined above should also be applied for observational studies. Here, we particularly emphasize the issue of total events again. Both, statistical power and robustness of data benefit from that approach, two reasons for frequently encountered limitations of negative findings in observational studies.<sup>37</sup>

### **Hierarchical testing**

A further point is the recent introduction of hierarchical testing of predefined endpoints. In an attempt to avoid multiple testing, it is considered fair not to use every endpoint separately. Recent examples include the ARISTOTLE trial of antithrombotics<sup>38</sup> and, more recently ODYSSEY OUTCOMES.<sup>8</sup> The finding of a reduction of all-cause mortality was published as an only “nominal significance”. The ambiguous reception in the scientific community

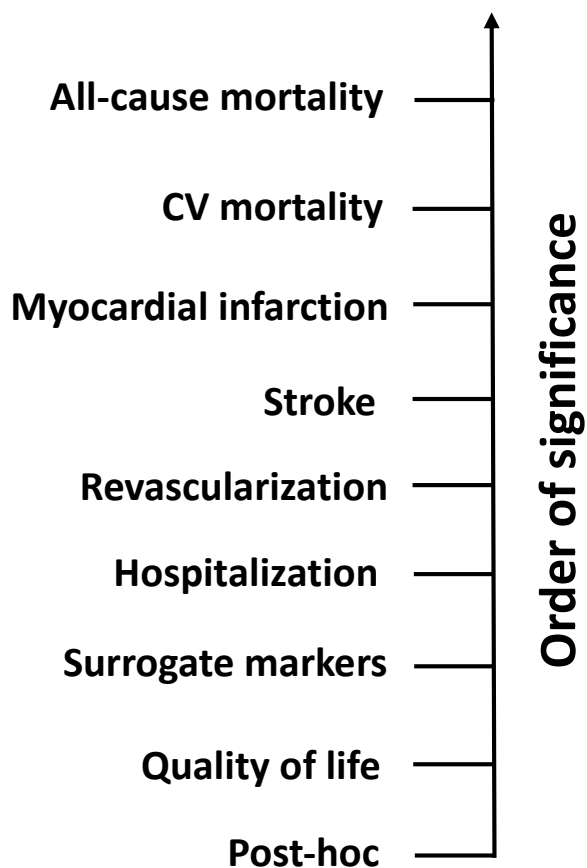
demonstrated that the sacrifice of the clinically most important endpoint (see *above*) simply for statistical purity is still a matter of debate.

### Questionnaires and quality of life assessment

Although well-being is of utmost importance for the patient, e.g. with heart failure or diabetes mellitus, this type of endpoint is soft and lacks objective measures. The perception of well-being by the patient is open for personal bias. Thus, quality of life is only rarely included in RCTs of cardiovascular drugs.<sup>39</sup>

Legend to Figure 1: CV .... cardiovascular

**Figure 1. Levels of endpoints in RCTs**



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