Surrogate End Points in Heart Failure Trials: Potentials and Limitations

Editorial

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Selection of end points for outcomes is an important step in a randomized clinical trial. The primary end point defines the research question and should ideally be clinically relevant, easily ascertained in all patients, capable of unbiased assessment, sensitive to the hypothesized effects of the treatment, and inexpensive to measure. Mortality is currently regarded as the most important true end point for evaluation of new heart failure drugs. However, the diminishing rates of these events in sequential trials means that progressively larger sample sizes are needed to display benefit from the next therapeutic agent. This explains the increasing use of composite end points and surrogate end points. The latter are substitutes for true end points for the purpose of comparing specific interventions in a clinical trial; they have no direct importance to the patient, but are biologically relevant and are supposed to show a strong and consistent relationship with clinical benefit. Another, perhaps more important, aspect is that surrogate end points increase our understanding of the disease process and mechanisms of action of drugs and thus may help take a more enlightened approach to managing patients. We review the potentials and limitations of the true and surrogate end points in clinical studies of patients with chronic heart failure.

The primary objectives in the treatment of patients with heart failure (HF) are to improve quality of life (QoL), delay the progression of the disease and increase survival. Randomized clinical trials represent the standard scientific method for assessing the efficacy of any treatment, and the basis for the approval of new drugs by governmental regulatory agencies.

The selection of the best response variables for the assessment of the efficacy of a treatment in HF patients is thus still under debate. Clinical trials conducted in thousands of HF patients with such agents as angiotensin-converting enzyme (ACE) inhibitors, β-receptor blockers, and aldosterone receptor blockers have succeeded in demonstrating incremental benefits on clinically relevant end points, particularly survival and freedom from hospitalization for HF. Although morbidity and mortality rates remain substantial in patients with HF, in the setting of clinical trials, a remarkable reduction in all-cause mortality is being observed. The diminishing rates of these events in
sequential trials have therefore mandated progressively larger sample sizes to display benefit from the next therapeutic agent. Therefore, the choice of an end point to show the benefit of an agent becomes very important. In this review, we briefly discuss the advantages and disadvantages of the common end points used in HF trials.

The primary end point of a trial should be clinically relevant, easily ascertainable in all patients, capable of unbiased assessment, sensitive to the hypothesized effects of the treatment, and inexpensive to measure. End points may be categorized as: (i) measures of clinical outcomes (eg, death or morbid events as hospitalization for worsening HF); (ii) measures of symptoms or clinical status (eg, quality of life, New York Heart Association [NYHA] class); or (iii) surrogates (eg, hemodynamic measurements, neurohormones, ventricular volumes and function).

MEASURES OF CLINICAL OUTCOMES

Mortality

Survival in HF clinical trials can be assessed by all-cause mortality, adjusted all-cause mortality, and cause-specific mortality. All-cause mortality is the most unbiased end point and has routinely been used in numerous HF clinical trials. A reduction in all-cause

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<thead>
<tr>
<th>TRAIL ACRONYMS</th>
<th>Description</th>
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<tbody>
<tr>
<td>A-HeFT</td>
<td>African-American–Heart Failure Trial</td>
</tr>
<tr>
<td>CAPRICORN</td>
<td>Carvedilol Post Infarction Survival Control in Left Ventricular Dysfunction</td>
</tr>
<tr>
<td>CHARM</td>
<td>Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity</td>
</tr>
<tr>
<td>COMET</td>
<td>Carvedilol Or Metoprolol European Trial</td>
</tr>
<tr>
<td>COMPANION</td>
<td>Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure</td>
</tr>
<tr>
<td>CONSENSUS</td>
<td>COoperative North Scandinavian ENalapril SUrvival Study</td>
</tr>
<tr>
<td>ELITE (I and II)</td>
<td>Evaluation of Losartan In The Elderly (first and second trials)</td>
</tr>
<tr>
<td>EVEREST</td>
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<td>MERIT-HF</td>
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<td>MOXCON</td>
<td>Effect of Sustained Release Moxonidine on Mortality and Morbidity in Patients with Congestive Heart Failure</td>
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<tr>
<td>VMAC</td>
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mortality, or alternatively another beneficial effect on symptoms or QoL, with assurance of no important increase in mortality, is important for regulatory approval of a drug. Although all-cause mortality has the advantage of being a “hard” end point, that is easy to measure, not readily subject to observer bias, and clearly represents an important event for the patients themselves, it has several limitations. The main concern of using only mortality as an end point is that it refers to the extreme manifestation of HF and occurs in only a small percentage of patients. Thus, most of the patients in the study do not contribute to a mortality end point, yet may have important QoL issues. Because the current management of HF has reduced the event rate considerably, if mortality is the primary end point, patients with advanced diseases have to be studied to get enough events for reasonable statistical power in a reasonable period of time. Consequently, patients in early stages of HF, in whom the disease process is most likely to be halted or possibly reversed, are not evaluated. Preventive strategy is therefore not assessed. Finally, trials using all-cause mortality as the primary end point require a large sample size to show a survival advantage of a new drug.

Adjusted all-cause mortality

Several trials have used adjusted all-cause mortality, to control for clinically relevant prognostic variables in Cox regression analyses. In the first Vasodilator–Heart Failure Trial (V-HeFT-I), mortality at the end of the study was lower at a borderline significance in the hydralazine/isosorbide (H/I) group compared with placebo using log-rank statistics. However, when a number of important baseline prognostic covariates, such as ejection fraction (EF), history of coronary artery disease, heart rate, and peak oxygen consumption were included in a Cox regression model, the reduction in mortality in the H/I group did reach statistical significance. In the Candesartan in Heart Failure Assessment of Reduction in Mortality and morbidity (CHARM) overall program, the unadjusted hazard ratio (HR) and 95% confidence interval (CI) for all-cause mortality was of borderline significance (HR, 0.91, 95% CI, 0.83 to 1.00, \( P=0.055 \)), but improved significantly (HR, 0.90, 95% CI, 0.82 to 0.99, \( P=0.032 \)) when adjusted for 33 predefined covariates. Whether the main treatment comparison should be adjusted remains a subject of debate. Adjustment may help to correct for unexpected baseline imbalance, and may increase statistical power. The covariates chosen should predict mortality and be prespecified in the primary analysis. Often, it is not possible to predict an imbalance at the beginning of the study. However, even a nonsignificant imbalance in a baseline covariate can matter if it is strongly related to mortality. In contrast, if the correlation with mortality is weak, even a statistically significant imbalance is unimportant.

Cause-specific mortality

Total mortality is classified into cardiovascular (CV) and non-CV mortality. CV mortality is further classified into cardiac and vascular. Cardiac death may be sudden and arrhythmic in nature, or result from pump failure and progressive HF. Although cause-specific mortality appears attractive, there are no “gold standard” definitions of different modes of death. The definition of sudden death, for instance, differs dramatically from one study protocol to another. Some trials have used a time-dependent definition, such as one hour since the onset of new symptoms, as was used in the COoperative North Scandinavian ENalapril Survival Study (CONSENSUS) and Evaluation of Losartan In The Elderly (ELITE) trials. The V-HeFT-I trial defined sudden death as either “observed to be instantaneous” or “unwitnessed, but assumed to be instantaneous on the basis of the clinical setting.” This heterogeneity of definition is also shared by death due to progressive HF and further complicated by the inclusion of “intermediate” classifications, such as death due to “HF or arrhythmias with HF” or “sudden death with worsening HF.” Thus, variations in definition often make comparison between trials difficult.

Table I (page 84) shows the mode of death in several landmark HF trials in patients with moderate- to-severe HF and low left ventricular (LV) EF. Despite differences in the definitions of mode of death, about 85% to 90% of all deaths were classified as CV deaths. The remaining 10% to 15% were non-CV deaths. Of the CV deaths, about 80% were classified as cardiac deaths

The opposite was the case for pump failure deaths that were more common in severe HF patients. Therefore, if an intervention, like an implantable cardioverter defibrillator (ICD), that is expected to reduce sudden death is being tested, the entire benefit is likely to be in that group. The major disadvantage of cause-specific mortality as an end point is that the mode of death has to be adjudicated. If sudden death can be
assessed accurately, then the use of sudden death as a cause-specific mortality end point would be the most sensitive outcome. Similarly, if a drug were expected to reduce cardiac or CV deaths as the primary outcome would be more appropriate and sensitive than the use of total mortality. Clearly, the added sensitivity conferred by using the CV cause-specific mortality as opposed to total mortality varies, depending on the proportion of all deaths that are expected to be CV. For example, in patients with a low EF and NYHA class IV end-stage HF such as those seen in the REMATCH trial (Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure),23 where over 95% (53 out of 54) of deaths were CV, the difference between using CV and total deaths is small, and use of all-cause mortality becomes a reasonable primary end point. On the other hand, in patients with HF and preserved EF where only approximately 60% of the deaths are CV,4,24-27 there could be an important increment in sensitivity by using CV deaths as opposed to total deaths as the primary end point. This is even more applicable in primary prevention trials where only about 50% of the events are classified as CV in such trials, use of cause-specific mortality is likely to significantly improve the sensitivity of end point measurement.

<table>
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<tr>
<th>Trials</th>
<th>Number of patients</th>
<th>Total mortality n (%)</th>
<th>Annual mortality rate (%)</th>
<th>Cardiovascular death n (%)</th>
<th>Sudden death n (%)</th>
<th>Pump failure death n (%)</th>
<th>Myocardial infarction death, n (%)</th>
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<td>118 (46.6)</td>
<td>33 (6 m)</td>
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<td>460 (47.8)</td>
<td>93 (9.7)</td>
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<td>520 (53.1)</td>
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<td>CHARM-Alt4</td>
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<td>561 (27.6)</td>
<td>7.5</td>
<td>471 (83.9)</td>
<td>191 (34)</td>
<td>159 (28.3)</td>
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<td>CHARM-Add4</td>
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<td>7.5</td>
<td>649 (82.3)</td>
<td>318 (40.3)</td>
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<td>313 (21)</td>
<td>19</td>
<td>243 (78)</td>
<td>83 (27)</td>
<td>139 (44)</td>
<td>10 (3.2)</td>
</tr>
</tbody>
</table>

*% of deaths by all deaths in each trial.
BET, Beta-blocker Evaluation Survival Trial.
CARE-HF, Cardiac Resynchronization in Heart Failure.
CHARM-Add, Candesartan in Heart Failure Assessment of Reduction in Mortality and morbidity-Added.
CHARM-Alt, Candesartan in Heart Failure Assessment of Reduction in Mortality and morbidity-Alternative.
CHF-STAT, Amiodarone in Patients with Congestive Heart failure and Asymptomatic Ventricular Arrhythmia.
COMPANION, Comparison of Medical, Pacing, and Defibrillation Therapies in Heart Failure.
CONSENSUS-1, Cooperative North Scandinavian ENalapril Survival Study.

Table 1. Mode of death in selected heart failure trials.
Hospitalizations for worsening heart failure

Worsening HF is an important end point in HF trials. However, identifying worsening HF clinically is often a challenge and most clinical trials have used hospitalization for HF to identify such events. Hospitalizations are generally adjudicated and classified into either cardiac or noncardiac. Cardiac hospitalizations are further categorized into those due to worsening HF, myocardial infarction, unstable angina pectoris, syncope, cardiac procedures, arrhythmia-based, heart transplantation, complications of cardiac medication or procedure, and other causes. Noncardiac causes include pulmonary, vascular, gastrointestinal, and renal causes, as well as noncardiac chest pain, cancer, hypovolemia, complications from noncardiac medication, and other nonspecific reasons.26 Whereas hospitalization as an end point represents a “hard” objective event, it is associated with its own limitations. The threshold for admission and duration of hospitalization differs among institutions and countries, depending in part on reimbursement or other governmental policies. Moreover, many patients who develop signs and symptoms of HF may not be hospitalized for these acute episodes, especially in institutions that use multidisciplinary chronic disease management programs. Therefore, these nonhospitalized episodes of HF may not be captured if hospitalization is a requirement to meet the HF end points. Furthermore, the definitions of HF hospitalization vary from study to study.29 Most clinical trials define hospitalization for HF as a hospital admission, or 24-hour observational stay with at least two signs and/or symptoms of HF and treatment with loop diuretics or intravenous vasoactive agents. Some trial protocols permit the use of IV therapy in the emergency room for at least a 4-hour period to be counted as a HF hospitalization.17 The SOLVD trial (Studies Of Left Ventricular Dysfunction) protocol also allowed significant increase in oral diuretic therapy in the hospital to be counted toward a HF event.10 Whereas use of IV diuretics identifies the high-risk patient, it may miss the low-risk patient, with important consequences to the outcome of a trial. For example, in the OVERTURE trial (Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events),30 the result of the primary end point of CV death or hospitalization for HF requiring IV diuretics changed from neutral (HR, 0.94; 95% CI, 0.86-1.03; P=0.19) to positive when the post hoc analysis used the SOLVD trial definition and included significant increase in oral diuretic therapy to be counted toward HF hospitalization (HR, 0.89; 95% CI, 0.82-0.98; P=0.012).

There are other challenges in the adjudication of worsening HF. Comorbidities often associated with HF like chronic obstructive pulmonary disease, atrial fibrillation, and renal dysfunction often make it difficult to assess whether the signs and symptoms of an acute event are due to worsening HF or worsening of the comorbidity.

CAUSE-SPECIFIC HOSPITALIZATIONS

In patients with moderate-to-severe HF and low EF, approximately 30% to 40% of all-cause hospitalizations are for worsening HF.28,31,32 This proportion decreases to around 20% to 25% in patients with less severe HF.33 Therefore, if a therapy is expected to reduce only HF hospitalizations, use of all-cause hospitalizations as the end point is likely to miss even a large decrease in HF hospitalization. For example, in the Val-HeFT trial (Valsartan–Heart Failure Trial), the use of valsartan was associated with a significant 28% reduction in HF hospitalizations, whereas all-cause hospitalizations were reduced by a nonsignificant 8% (P=0.15). In this case, the selection of cause-specific hospitalizations for HF helped to increase the sensitivity and statistical power. However, the drug being tested might reduce HF hospitalizations, but increase hospitalizations for another cause such as cancer. Therefore, recording of all-cause hospitalization serves as an important safety end point. Another problem in using all-cause hospitalizations arises when the protocol only counts the first hospitalization in a time-to-event analysis. Consider a patient whose first hospitalization is for gallbladder surgery and 6 months later is readmitted for worsening HF. If the protocol is focused only on time to first hospitalization, then the hospitalization for HF would be missed. In SOLVD,32 approximately 38% of hospitalizations for HF occurred after a hospitalization for another cause. Therefore, considering time to first all-cause hospitalization could lead to a loss in statistical power by inclusion of events that are insensitive, and to loss in events that are truly sensitive to the treatment effect.

When a drug or device reduces mortality, the unbiased evaluation of recurrent hospitalizations becomes a challenge due to differential follow-up time between comparison groups and the competing risk of mortality. Therefore, statistical comparisons of hospitalization burden that are not adjusted for follow-up time, mortality, and/or multiple hospitalizations can be biased and misleading. It is well known that the likelihood of hospitalization and death are related. For example, death removes the sickest patients who are
likely to be hospitalized, whereas a hospitalization increases the risk of death as well as the risk of subsequent hospitalization (Figures 1 and 2). Therefore, a difference in hospitalization rate between treatment groups could solely be due to differences in survival rather than a specific effect of the treatment on hospitalizations per se. Fortunately, sophisticated nonparametric methods are available that take into consideration mortality as a competing risk while also adjusting for follow-up time and multiple hospital admissions per patient. In the COMPANION trial, the use of cardiac resynchronization therapy (CRT) reduced death rates as compared with optimal medical therapy alone.

This would be expected to lower the risk of hospitalization in the optimal medical therapy group, because the sickest patients died and were no longer at risk of hospitalization. Thus, the treatment effect of the device on hospitalizations is attenuated if an adjustment is not made for the competing risk of death (Figure 3). In the Second Multicenter Automatic Defibrillator Implant Trial (MADIT II), the use of an ICD was associated with significant decrease in mortality; however, this was accompanied by an increase in the first and recurrent HF events (adjusted hazard ratios of ICD versus placebo were 1.39 ($P=0.02$) and 1.58 ($P<0.001$), respectively). It is possible that if the MADIT II investigators had analyzed the data by taking into account the competing risk of mortality and differences in follow up time, the results may have been different.

MEASURES OF SYMPTOMS OR CLINICAL STATUS

Quality of life

OQoL questionnaires, which provide comprehensive information about the effects of a disease and its treatment on patients’ lives, are now widely used in clinical trials. The OQoL questionnaires can be general or disease-specific, and there is no general agreement as to which type of questionnaire is most appropriate. Few questionnaires have been validated in HF patients in a way that shows that the results correlate with the severity of disease.

Many ongoing studies on the treatments of chronic HF incorporate the Minnesota Living with Heart Failure Questionnaire (MLHFO) (Table II) as a measure of...
QoL. Statistically significant improvements in the QoL score have been observed in placebo-controlled studies of enalapril, flosequinan, pimobendan, vesnarinone, and valsartan. However, flosequinan, pimobendan, and vesnarinone have also been shown to have an adverse effect on survival, raising the issue of a trade-off between improved QoL and the risk of drug-induced death. Increased mortality with these and other agents clearly indicates that symptomatic benefit in HF does not necessarily predict improved survival.

**Figure 3. Hospitalization curves.** Hospital admission rate per patient is stratified by treatment arm.

Abbreviations: CRT, cardiac resynchronization therapy; CRT-D, CRT in combination with a defibrillator; CRT-P, CRT alone; OPT, optimal pharmacological therapy.


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**Table II. Minnesota Living with Heart Failure Questionnaire.**

New York Heart Association functional class

The New York Heart Association (NYHA) classification is a 4-point semiquantitative index of functional status of patients with HF. NYHA class is widely accepted and useful clinically because it correlates with quality of life and survival. When measured serially over time, it provides a means of tracking disease progression and response to therapeutic interventions. Although it is “subjective,” NYHA class has also been used in many clinical trials as a demonstration of efficacy for both pharmacologic and device interventions.

To overcome the “subjective” nature of NYHA classification, various quantitative and objective measurements of functional capacity have been developed in recent years. Although most physicians are experienced in assigning a NYHA class, the method of assignment is not standardized and the reproducibility of determining NYHA class has never been established. Concerns have also been raised about unblinding. Kubo et al developed a patient questionnaire to determine NYHA classification within the context of clinical trials where blinded conditions are not possible. Goldman et al developed a specific activity scale in which the patient’s functional class was based on the estimated metabolic cost of different activities. However, the output of the specific activity scale was not exactly analogous to NYHA and many of the queries did not appear to be relevant to a contemporary population.

Exercise capacity

6-minute walk test

The 6-minute walk test was found to predict long-term mortality and HF hospitalization rates in patients with LV dysfunction of varying cause and severity. The test can be administered safely in an outpatient setting without specialized equipment and is well accepted by patients. Although the 6-minute walk test has been used as an outcome measure in more than 60 randomized clinical trials since 1988, its ability to distinguish between effective or ineffective interventions in patients with HF has not been fully explored. Some data have not confirmed the predictive value of the distance walked on survival, especially in patients with mild HF and preserved exercise tolerance. Olson et al performed a systematic literature review investigating the utility of the 6-minute walk test as a measure of the effectiveness of treatment in randomized controlled trials of HF and found that the test has not yet been proven to be robust enough for the identification of effective pharmacological interventions. Likewise, it has proved useful in some, but not in other studies that assessed CRT. The 6-minute walk distance is therefore considered helpful in clinical descriptions of HF patients, but cannot be used as a surrogate marker for assessing survival in HF trials.

Treadmill or cycle exercise testing

Treadmill or cycle exercise testing has generally shown that therapeutic interventions that lessen symptoms in HF patients also improve exercise tolerance and, conversely, that symptomatically ineffective drugs produce little change in exercise capacity. Exercise tolerance, expressed as exercise time or workload achieved on an ergometer, has been recognized for several decades as an important prognostic marker in patients with heart disease.

Peak VO2

In recent years, there has been increased interest in directly measured maximal oxygen uptake (peak VO2) during exercise. Peak VO2 has been considered by some investigators as the best criterion of exercise capacity in patients with chronic HF. As an objective measure of maximal exercise capacity, peak VO2 has been found to be an independent prognostic indicator in HF. In some HF trials, change in peak VO2 has been used to assess the effectiveness of the intervention.

Some therapeutic interventions in HF that increase exercise capacity also improve survival. However, an improvement in survival has not been demonstrated with every therapeutic agent that improves effort tolerance. Results from the Prospective Randomized Milrinone Survival Evaluation (PROMISE) and Randomized Evaluation of FLosequinan on ExerCise Tolerance (REFLECT) trials have shown that early treatment-induced improvements in exercise tolerance were unreliable predictors of actual treatment effects on survival.

Surrogate end points in chronic heart failure trials

Surrogate end points are those that are not direct measures of clinical outcome, symptoms, or clinical status, but correlate with clinically relevant findings, either because they signal worsening of the underlying disease or contribute to its pathophysiology. A valid surrogate should have a strong consistent and biologically relevant relationship with survival and should unequivocally reflect the true end points (ie, survival.
HF, endothelial dysfunction as a surrogate end point for coronary artery disease, and serum creatinine and natriuretic peptide levels as a surrogate end point for gate end points for patients with HF. The role of B-type natriuretic peptide (BNP) and brain natriuretic peptide (BNP) in HF progression has been extensively studied. These peptides are increased in response to cardiac overload and are used as diagnostic markers for HF.

Surrogate end points have several potential advantages. Clinical trials evaluating surrogate end points can provide an answer about the effectiveness of a drug or device with a smaller sample size, in a shorter duration, and are therefore less expensive to run. Unlike mortality, which only provides an average response in a population, surrogate end points assess efficacy in every individual and can assess early stages of the disease. The principal disadvantage of using surrogates to assess therapies is the possibility of an incomplete, inadequate, or misleading evaluation and the fact that they do not assess long-term safety of the drug or device. Drugs usually have multiple effects, and resorting to a single surrogate end point, focused exclusively on one intermediate effect, often precludes the evaluation of other intended or unintended health effects. Currently, regulatory agencies do not accept surrogate end points for approval of drugs for the treatment of HF. Nevertheless, surrogate outcomes are important and indispensable in the early development of drugs and devices and in establishing a “proof of concept.”

Chronic heart failure (CHF) is the final common pathway of several processes involved in the cardiovascular continuum that is initiated by risk factors for cardiovascular diseases. Once initiated, cardiovascular disease progresses through structural remodeling of the heart and blood vessels. Factors that contribute to this include activation of various neurohormones, growth factors, and cytokines. Markers of this biological process (e.g., LV hypertrophy and enlargement) and factors that contribute to it (e.g., neurohormones) may be viewed as surrogates of the progression of the disease.

More than 150 clinical, hemodynamic, or exercise variables correlate with survival in patients with HF. However, “a correlate does not a surrogate make.” Only some of these variables have been tested in clinical trials as surrogates, and none have been completely validated. We will only briefly focus on hemodynamic measurements, neurohormones, and variables of LV structure and function (remodeling) as potential surrogate end points for HF. Endothelial dysfunction as a surrogate end point for coronary artery disease, and serum creatinine and microalbuminuria as surrogate end points for renal dysfunction will be detailed in the following Expert Answers section of this Journal.

**Hemodynamic measurements**

During the 1980s, HF was considered primarily a hemodynamic disorder, and physicians believed that therapeutic interventions that improved pump function would predictably benefit patients. Invasive hemodynamic studies to assess cardiac output and right and LV filling pressures were viewed as crucial in development programs for new drugs. Later studies, however, have raised important concerns about the validity of acute hemodynamic changes as surrogate end points. A number of controlled clinical trials conducted since the 1990s have shown that drugs like milrinone, pimobendan, flosequinan, flolan, vesnarinone, and levosimendan, which produce striking hemodynamic benefits, do not necessarily produce long-term clinical benefits and may be associated with increased mortality. More recently, in the Vasodilation in the Management of Acute CHF (VMAC) study, when the recombinant human brain natriuretic peptide nesiritide was added to standard care in patients hospitalized with acutely decompensated CHF, the hemodynamics and some self-reported symptoms improved more with nesiritide than intravenous nitroglycerin or placebo. In another report by the Nesiritide Study Group, nesiritide significantly reduced the pulmonary capillary wedge pressure and clinical status. However, follow-up data on these subjects, which were not part of the study design, suggested that nesiritide may have had an adverse effect on 30-day mortality and a greater deterioration in renal function as compared to those given placebo. These findings have discouraged the use of hemodynamic variables as surrogate markers for drug efficacy. However, the converse is not true. All the drugs approved for treatment of HF have long-term beneficial hemodynamic effects, and there are no drugs that worsen hemodynamics and improve long-term outcomes.

**Neurohormones**

Several neurohormones play an important role in the pathogenesis and progression of HF. Two sets of neurohormones with opposing effects are activated in the syndrome of HF. The vasoconstrictor hormones are antinatriuretic, antidiuretic, and generally have growth-promoting properties, whereas the vasodilator hormones are natriuretic, diuretic and have antimitogenic effects. Norepinephrine (NE) and the natriuretic peptides are the most studied neurohormones in HF, and
the strongest evidence for their pathogenetic role comes from studies showing that modulation of these neurohormones is associated with changes in clinical course and survival.

Measurements of plasma NE were performed in the Second Vasodilator–Heart Failure Trial (V-HeFT-II) to examine the effects of therapy on neuroendocrine activation and the responses to therapy among patients with different degrees of activation. The baseline plasma NE data were grouped into three relatively homogeneous strata: plasma NE <600 pg/mL, 600 to 900 pg/mL, and >900 pg/mL. Cumulative mortality was found to differ significantly between strata: NE values <600 pg/mL were associated with the lowest risk, values between 600 and 900 pg/mL were associated with an intermediate risk, and values >900 pg/mL identified a group at exceedingly high risk. The group treated with enalapril had a significantly lower mortality than the group treated with hydralazine-isosorbide dinitrate, and this benefit was most evident in patients with NE values >900 pg/mL. Similarly, in the CONSENSUS trial, significant reduction in mortality seen with enalapril was confined to patients with baseline NE levels above the median. Other studies have raised important concerns about the validity of plasma NE as a surrogate marker in HF treatment trials. In the Australia–New Zealand Carvedilol Heart Failure Trial, high baseline NE levels did not predict additional survival benefit with carvedilol, which significantly reduced HF admissions only in those patients with NE levels below the median. The most worrisome examples of disagreement between survival data and plasma NE values come from studies with ibopamine and moxonidine. The PRIME II (Second Prospective Randomized Study of Ibopamine on Mortality and Efficacy) and MOXCON (Effect of Sustained Release Moxonidine on Mortality and Morbidity in Patients with Congestive Heart Failure) trials were terminated prematurely because of the adverse effects of ibopamine and moxonidine on mortality despite significant reductions in plasma NE. These results limit the use of plasma NE as a surrogate marker for HF trials.

### Ventricular remodeling

It is now generally recognized that heart failure progresses through a process of structural remodeling of the heart (Figures 4 and 5) to which neurohormonal and cytokine activation make an important contribution. A number of studies have demonstrated a strong and independent correlation between ventricular dilation and subsequent mortality, particularly among patients who have suffered a myocardial infarction.

More importantly, agents that have beneficial effects in HF also generally attenuate or reverse ventricular remodeling, whereas agents that have failed to improve clinical outcomes either had no effect on remodeling or have been associated with adverse remodeling. V-HeFT-I and V-HeFT-II were the earliest studies to show that drugs like the hydralazine-isosorbide dinitrate combination and enalapril, which improved survival, also slowed remodeling, whereas prazosin had no effect on remodeling or outcomes.

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**Figure 4. Left ventricular (LV) remodeling over time.**

Left ventricular angiogram in the right anterior oblique projection of a patient 1 month after acute myocardial infarction (March 1996) and 2 years later (April 1998). Note that 2 years after infarction, the end-diastolic volume (EDV) was 5 times normal, end-systolic volume (ESV) was 5 times normal, stroke volume (SV) was decreased, and there was a further decrease in ejection fraction (EF). There was a decrease in the ventricular mass-to-volume ratio over time, suggesting further increase in wall stress. The globular shape contributed to severe mitral regurgitation.


**Figure 5. Ventricular remodeling in systolic and diastolic heart failure as a function of time.**

Subsequently, several studies have confirmed the strong association of improvement in ventricular remodeling and long-term outcomes. Table III lists a number of clinical trials that tested the effect of drugs and devices on clinical outcomes and their effect on ventricular remodeling. Table IV compares the echocardiographic, nuclear, and MRI techniques in assessing remodeling in heart failure. Most measurements of LV remodeling were made in substudies of the morbidity and mortality trial. However, very few studies have reported the effect of the intervention on remodeling and outcomes in the same patient population. Nevertheless, the data do show that in every case, the survival effects, unknown at the time that the volumetric data were acquired, paralleled the changes in ventricular remodeling.

### Table III. Relationship between drug effects on left ventricular remodeling and on mortality in heart failure.

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>Left ventricular size and volumes</th>
<th>Mortality and morbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOLVD Treatment</td>
<td>Enalapril</td>
<td>Reduced&lt;sup&gt;97&lt;/sup&gt;</td>
<td>Reduced&lt;sup&gt;10&lt;/sup&gt;</td>
</tr>
<tr>
<td>SOLVD Prevention</td>
<td>Enalapril</td>
<td>Mildly reduced&lt;sup&gt;98&lt;/sup&gt;</td>
<td>Mildly reduced&lt;sup&gt;111&lt;/sup&gt;</td>
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<tr>
<td>SAVE</td>
<td>Captopril</td>
<td>Reduced&lt;sup&gt;99&lt;/sup&gt;</td>
<td>Reduced&lt;sup&gt;112&lt;/sup&gt;</td>
</tr>
<tr>
<td>ANZ Carvedilol Trial</td>
<td>Carvedilol</td>
<td>Reduced&lt;sup&gt;100&lt;/sup&gt;</td>
<td>Reduced&lt;sup&gt;100&lt;/sup&gt;</td>
</tr>
<tr>
<td>MERIT-HF</td>
<td>Metoprolol CR/XL</td>
<td>Reduced&lt;sup&gt;101&lt;/sup&gt;</td>
<td>Reduced&lt;sup&gt;16&lt;/sup&gt;</td>
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<tr>
<td>CAPRICORN</td>
<td>Carvedilol</td>
<td>Reduced&lt;sup&gt;102&lt;/sup&gt;</td>
<td>Reduced&lt;sup&gt;113&lt;/sup&gt;</td>
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<tr>
<td>RALES</td>
<td>Spironolactone</td>
<td>Reduced&lt;sup&gt;103&lt;/sup&gt;</td>
<td>Reduced&lt;sup&gt;21&lt;/sup&gt;</td>
</tr>
<tr>
<td>Val-HeFT</td>
<td>Valsartan</td>
<td>Reduced&lt;sup&gt;104&lt;/sup&gt;</td>
<td>Reduced&lt;sup&gt;17&lt;/sup&gt;</td>
</tr>
<tr>
<td>A-HeFT</td>
<td>Isosorbide dinitrate/hydralazine</td>
<td>Reduced&lt;sup&gt;105&lt;/sup&gt;</td>
<td>Reduced&lt;sup&gt;14&lt;/sup&gt;</td>
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<tr>
<td>PRIME II</td>
<td>Ibopamine</td>
<td>Increased&lt;sup&gt;106&lt;/sup&gt;</td>
<td>Increased&lt;sup&gt;85&lt;/sup&gt;</td>
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<tr>
<td>ELITE-II</td>
<td>Losartan vs captopril</td>
<td>Trend favored captopril&lt;sup&gt;106&lt;/sup&gt;</td>
<td>Trend favored captopril&lt;sup&gt;115&lt;/sup&gt;</td>
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<tr>
<td>OVERTURE</td>
<td>Omapatrilat vs. Lisinopril</td>
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<td>Neutral&lt;sup&gt;30&lt;/sup&gt;</td>
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<tr>
<td>RENAISSANCE</td>
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<td>Reduced&lt;sup&gt;18&lt;/sup&gt;</td>
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</table>

**Abbreviations:** MRI, magnetic resonance imaging; RVG, radionuclide ventriculography.


![Table IV](https://example.com/tableIV.png)
In SOLVD, the relative benefit of enalapril versus placebo on ventricular remodeling approximated the relative benefit on outcomes, although this was not tested in the same population. \(^{10,97,98,111,119}\) Similar correlations were also seen with the use of captopril between mortality and morbidity end points and LV remodeling in the Survival And Ventricular Enlargement (SAVE) trial.\(^{92,99,112}\) In the MESToprolol Randomized Interventional Trial in Heart Failure (MERIT-HF), the antiremodeling effects of metoprolol CR/XL on the left ventricle seen in the MRI substudy\(^{103}\) paralleled the decrease in mortality from worsening HF.\(^{16}\) In the Australia-New Zealand trial of carvedilol in patients with ischemic cardiomyopathy,\(^ {100}\) and in the Carvedilol Post Infarction Survival Control in Left Ventricular Dysfunction (CAPRICORN) trial, carvedilol had a beneficial effect on ventricular remodeling\(^{102}\) and reduced CV mortality.\(^{113}\)

In a meta-analysis, carvedilol showed greater benefits on LV remodeling compared with immediate-release metoprolol,\(^ {120}\) a finding that anticipated the subsequent results of the Carvedilol Or Metoprolol European Trial (COMET) showing improved survival for patients randomized to carvedilol, compared with those randomized to immediate-release metoprolol.\(^ {121}\) RALES showed a 30% reduction in mortality with spironolactone in patients with advanced HF.\(^ {21}\) A later study showed improvement in LV volume and mass with spironolactone.\(^ {103}\) In the Val-HeFT trial, beneficial effects of valsartan on the first morbid event in the overall population were associated with reduction in LV size and improvement in left ventricular ejection fraction (LVEF).\(^ {17,104}\) In the African American Heart Failure Trial (A-HeFT), therapy with the isosorbide dinitrate/hydralazine combination resulted in regression in LV remodeling\(^ {105}\) and increased survival among black patients with advanced HF.\(^ {114}\)

Ibopamine was initially observed to increase ventricular volumes,\(^ {86}\) and later found to be associated with excess mortality.\(^ {85}\) The angiotensin receptor blocker losartan was initially found to have a smaller effect on LV volumes compared with the ACE inhibitor captopril,\(^ {106}\) and later the ELITE-II study found that mortality also tended to be lower with captopril.\(^ {115}\) A comparison of lisinopril\(^ {122}\) and the dual vasopeptidase inhibitor omapatrilat found an equivalent effect on both these drugs on mortality\(^ {30}\) and LV remodeling\(^ {107}\) (OVERTURE trial). In the RENAISSANCE trial (Randomized Etanercept North American Strategy to Study ANtagonism of CytokinEs), the use of the soluble tumor necrosis factor antagonist etanercept had no effect on mortality or LV mass and volumes measured with MRI.\(^ {116}\) Despite favorable early clinical findings,\(^ {123,124}\) endothelin receptor antagonist use has been associated with neutral to adverse effects on clinical outcomes and no benefits on LV volume or mass.\(^ {108}\)

We have shown earlier that chronic arginine vasopressin receptor blockade does not attenuate post-myocardial infarction ventricular remodeling in the rat model.\(^ {125}\) In a well-treated population of stable HF patients, there was no significant effect of tolvaptan therapy on LV volumes observed during 1 year of therapy.\(^ {109}\) In the Efficacy of Vasopressin antagonism in hEart failuRE: outcome Study with Tolvaptan (EVEREST) trial,\(^ {117}\) tolvaptan initiated for acute treatment of patients hospitalized with HF had no effect on long-term mortality or HF-related morbidity. CRT is associated with improvement in mortality and morbidity\(^ {18}\) and reverses ventricular remodeling.\(^ {18,110}\)

Changes in LV remodeling over time have also been shown to correspond generally to subsequent changes in mortality, independent of drug effect.\(^ {92,96,126}\) Recently, Kramer et al.\(^ {127}\) reported the effects of a drug or device on remodeling and mortality in 68,481 patients with LV dysfunction included in 30 large-outcome randomized clinical trials of 24 distinct drug/device therapies and in 14,808 patients included in 89 remodel-

![Figure 6. Placebo-corrected change in end-diastolic volume (EDV) from randomized clinical trials (RCT) plotted against the mortality odds ratio for the specific therapy.](image_url)

**Figure 6.** Placebo-corrected change in end-diastolic volume (EDV) from randomized clinical trials (RCT) plotted against the mortality odds ratio for the specific therapy.

ing trials. The odds ratios for death in the outcome randomized clinical trials correlated significantly with drug/device effects on LV volumes and EF (Figure 6).

However, there are no studies that have shown that a particular relative magnitude of change in ventricular remodeling is associated with similar relative magnitude of benefit on outcomes in the same population. Thus, further studies are required to reinforce the role of remodeling as a credible surrogate marker in HF trials.

## COMPOSITE END POINTS

With the diminishing rates of mortality events, the use of composite end points has become common in HF trials. A composite or combined outcome is defined as “an event that is considered to have occurred if any one of several different events or outcomes is observed.” Each component of a composite end point should be clinically relevant and sensitive to the hypothesized effect of the treatment, and must be easy to be determined. Composite end points may comprise any combination of clinical or surrogate end points. Table V shows the advantages and disadvantages of different primary end point choices. If the treatment effect is similar for each component of the composite outcome, the event rate in a trial will increase. That would help to reduce the sample size, increase the power and decrease the duration of the study. If, however, the treatment does not have a similar effect on all the composites, the power can actually decrease.

The composite end points become difficult to interpret if the treatment effects go in the opposite direction for some components or if the effect of treatment is primarily on a more common, less serious component of the composite. Composite outcomes are typically analyzed as time to first event. As discussed in the cause-specific hospitalization section above, this could lead to a substantial loss of information because the events after the first are not counted. Therefore, when composite end points are used, data on all subsequent events that are part of the composite should be collected and evaluated separately as secondary end points. In the CHARM-Added, Alternative, and Preserved trials, the primary outcome was the composite of cardiovascular death or hospitalization for HF analyzed as time to the first event. However, all the components of the composite primary end point were separately analyzed as secondary end points. In the COMPANION trial, the primary end point was the composite of death from any cause or hospitalization from any cause. The A-HeFT trial used a unique composite score of weighted values for all-cause mortality, first hospitalization for HF, and change in QoL after 6 months. The time-to-event analysis was not used. Each component of the end point was given a score, with death getting the worse score, followed by hospitalization and change in QoL. There are several advantages of such a composite: each patient contributes to the end point and it integrates the QoL with clinical outcomes. The main disadvantages of this scoring system are that the time to death or hospitalization is not taken into account, the weight assigned to each component is arbitrary and not dependent on any objective criteria, and the relative importance of each component is subjective. Moreover, the score has not been validated in other trials.

### Table V. Advantages and disadvantages of different primary end point choices.

<table>
<thead>
<tr>
<th>Advantage</th>
<th>Disadvantage</th>
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<td>Single outcome</td>
<td>Simple</td>
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<tr>
<td>Single combined end point</td>
<td>Sample size</td>
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<td>Co-primary outcomes</td>
<td>Eggs not all in one basket</td>
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<tr>
<td>Global index</td>
<td>Power</td>
</tr>
<tr>
<td>Hierarchichal scoring/ranking</td>
<td>Power; clinical relevance</td>
</tr>
</tbody>
</table>


## The role of the clinical event committee in a cardiovascular outcome study

Identification of clinical events is critical to the integrity of the clinical research process, but accurately classifying clinical events can be problematic. Debate about classification of events has changed the interpretation of some study results and undermined the validity of a study. Many studies have relied on medical records, death certificates and interpretation of the site principal investigator to establish a clinical event, but the utility of these source documents may be limited due to inconsistencies and omissions in the recording of important details. In prospective studies, disagreement between independent reviewers can occur despite predefined criteria, casting uncertainty on end point assessment. Many prospective clinical trials have used clinical event committees (CECs) to blindly adjudicate the occurrence of an end point using crite-
ria defined at the outset of the trial. Heagerty et al.\textsuperscript{134} recently examined the role and usefulness of CECs in examining all events in the International Nifedipine once-daily Study Intervention as a Goal in Hypertension Treatment (INSIGHT). More than 28% of investigator-coded primary events and more than 41% of secondary events were reclassified by the CEC. These findings support the use of CECs for end point adjudication in any large outcome clinical trial.

**CONCLUSIONS**

In the design of clinical trials, choice of the most appropriate primary outcome measures is crucial. Although all-cause mortality is a simple and most unbiased end point that is easy to measure, not subject to observer bias, and clearly represents an important event for the patient himself, it has several limitations. Mortality is the extreme manifestation of HF and because it occurs in only a small percent of subjects, most patients do not contribute to a mortality end point. Trials using mortality as the primary end point require a large sample size to show a survival advantage of a new drug. Moreover, patients in early stages of HF, in whom the disease process is most likely to be halted or possibly reversed, are not evaluated. Preventive strategy is therefore not assessed.

To understand whether a treatment makes patients feel better and live longer and out of hospital, incorporation of clinical (QoL, mortality, hospitalization), functional, structural, and laboratory outcomes may provide a powerful and meaningful composite end point in some cases. Use of a composite end point also results in a smaller sample size and reduces the duration of the trial if the treatment effect is similar on all the components of the composite. However, there is little agreement on the most appropriate composite end point and the criteria to define a meaningful effect on the composite. There is, therefore, urgent need for a consensus among the trialists and the regulatory authorities on some of these issues.

Surrogate end points are physiologic variables that are known to be statistically associated and are believed to be pathophysiologically related to the clinical outcome. Use of surrogate end points in clinical trials offers many potential advantages: fewer patients, shorter follow-up, and lower cost. However, use of surrogates requires a clear understanding of the relationship—both physiologic and statistical—between the surrogate and the clinical results that are presumed to follow. Demonstration of “efficacy” based on surrogate results must be further subjected to analysis of risk-benefit, because serious adverse events may negate an intervention’s clinical utility. An appropriate approach may be to integrate surrogate end points with clinical measures through use of composites, allowing the surrogate finding to augment the clinical outcome, which might otherwise not be definitive on its own. Currently, regulatory agencies do not accept surrogate end points for approval of drugs for the treatment of HF and require that new therapies address clinically relevant outcomes before approval. The recent concerns about well-established surrogate end points such as reduction in cholesterol and glucose support such policies.\textsuperscript{135-137}

The putative role of B-type natriuretic peptides as surrogate end points for HF, as well as endothelial dysfunction as a surrogate end point for coronary artery disease and serum creatinine and microalbuminuria as surrogate end points for renal dysfunction will be detailed in the following Expert Answers section of this Journal.

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SURROGATE END POINTS IN HEART FAILURE TRIALS: POTENTIALS AND LIMITATIONS

Surrogate is a word that has many meanings—or, rather, the meaning is simple and straightforward: all it is really is just another word for “substitute” (in other words, it’s a substitute for substitute…). But this simple meaning applies to many different situations that are often quite arcane for the layperson: a surrogate model (used in engineering), a Surrogate Court (a type of law court), a surrogate proxy (referring to a variety of server in computer sciences), and many others.

However, there is one situation where the word is much in the public eye these days, and that is “surrogate motherhood” and the ongoing debate around the ethical issues it raises. It does not fall within the purview of this journal to fuel that particular debate, but one parallel can be drawn: there is just as heated a debate among cardiologists around the concept and use of “surrogate end points” in clinical trials, and particularly so in the context of heart failure trials.

So how do “surrogate end points” (which the National Institutes of Health [NIH] define as “a biomarker intended to substitute for a [real] clinical end point”) enter the picture in heart failure? A recent editorial in Dialogues (2009;14:No. 2) on cardiovascular disease prevention, proudly recalled that 6 out of the 8 years of extended life expectancy enjoyed by affluent societies over the past century were directly attributable to advances in cardiology.

However, this sunny outlook must be tempered by two caveats. First of all, the problem of cardiovascular disease and cardiovascular mortality has by no means been solved. Cardiovascular mortality is still the number one killer worldwide and will continue to be so until the year 2030 at least. In actual fact, cardiological success has often meant merely delaying cardiovascular mortality, for example by transforming an acute disease into a chronic one. On other occasions, it has meant replacing one evil with another: thus the success of reperfusion means that today one is far less likely to die from a myocardial infarction than from its sequelae, chief among which is heart failure. So the fight must go on to find ever better treatments and procedures. And this is where the second caveat comes in. In a sense, cardiology is suffering from its own success.
Better drugs and better procedures are increasingly more difficult to develop because we are trying to improve on an improvement. This requires randomized controlled trials, in which the trial drug has to prove effectiveness against already effective background therapies. Thus, because the frontiers of cardiovascular mortality have been so successfully pushed back, clinical trials with cardiovascular end points are becoming increasingly difficult because they need more patients or a longer follow-up for the results to be statistically meaningful. This means, too, that they are becoming ever more expensive. In turn, this has implications for the pharmaceutical industry: because of the increased length of studies, a huge share of the patent life of cardiovascular drugs is taken up by the drug development process so that its “market life” has shrunk to the current average of 6 to 8 years. As a result, pharmaceutical companies are finding it increasingly hard to make their investment in research financially sustainable, and several of them are considering reducing financial investments in cardiovascular research and allocating their funds instead to other areas where the length of studies and numbers of patients are more manageable, such as cancer research, for example. Clinical trials for cardiovascular drugs thus are at risk of simply pricing themselves out of existence. Thus, while all agree that cardiovascular research should continue, the real question is whether it will be able to continue, in terms of economic sustainability.

There is therefore a crying need to find alternative and reliable ways to test cardiovascular drugs, and particularly so where the needs are among the greatest: in heart failure, which is the price cardiology is paying for its own success. One of these ways is to use surrogate end points, and this is what this issue of Dialogues is all about. Many surrogate end points have been proposed, but here more than anywhere else in medicine the saying applies: “Many are called but few are chosen.” As stated by Desai and Temple (AAPS J. 2006;8:E146-E152) “Only a small minority of biomarkers are established surrogate end points; blood pressure is an example of a surrogate end point accepted by both clinicians and regulators. It was a plausible surrogate because of the large epidemiologic databases demonstrating a correlation between elevated blood pressure and adverse cardiovascular measures.” This issue of Dialogues will focus on two of the most promising surrogate end points in heart failure: brain natriuretic peptides and endothelial dysfunction. But alongside potentials there are also limitations, and surrogate end points have their downside: each surrogate has its cutoff point below which, while still reflecting an “abnormality,” it no longer is reliably predictive. Also, overreliance on surrogate end points in the end risks promoting a sort of treatment based on “numbers” rather than on clinical reasoning. This issue of Dialogues also looks into this delicate issue.

Obviously, it is too early to substitute surrogate end points for hard end points. However, the scientific community and clinical trial regulators cannot ignore the problem and Dialogues in Cardiovascular Medicine is proud to contribute to the debate.
Surrogate End Points in Heart Failure Trials: Potentials and Limitations

Expert Answers to Three Key Questions

1

Can BNP or NT-pro-BNP be considered surrogate end points for heart failure?

T. A. McDonagh

2

Could endothelial dysfunction be a surrogate end point for coronary artery disease?

M. Wolfrum, I. Sudano, J. Steffel, T. F. Lüscher

3

Can there be any surrogate for safety?

M. A. Pfeffer, H. Skali
Can BNP or NT-pro-BNP be considered surrogate end points for heart failure?

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Given the recent history of clinical trials of novel interventions for heart failure (HF), in particular new drug treatments, it would be immensely appealing to be able to use a robust surrogate end point that might reduce the size, time, and expense of conducting randomized clinical trials. Managing to move away from conventional mortality and morbidity end points would be particularly useful in chronic systolic HF studies where new drugs are being tested on top of extremely efficacious baseline therapy.

So what is a surrogate end point? In clinical trial terminology it is defined as a “measure of effect of a certain treatment that may correlate with a real end point, but doesn’t necessarily have a guaranteed relationship.” The US National Institutes of Health have also stated that a surrogate end point is “a biomarker intended to substitute for a clinical end point.”

There are a number of potential surrogate end points for the complex syndrome of HF. As HF is not a disease entity in itself, but a clinical syndrome arising as a result of numerous cardiac pathologies, it is a tough task to find a good surrogate for the morbidity and mortality that are constant hallmarks of the presence of HF. Numerous neurohormonal markers, cytokines, hemodynamic parameters, and imaging measures of remodeling have been suggested. However, the B-type natriuretic peptides (B-type NPs, formerly known as brain natriuretic peptides [BNP]) have emerged as the strongest contenders for such surrogate status.

This article reviews the credentials of B-type NPs as a surrogate end point for HF.

**B-TYPE NATRIURETIC PEPTIDES AND HEART FAILURE**

The family of B-type NPs consists of two circulating forms, the inactive N-terminal fragment (NT-pro-BNP) and the active peptide (BNP) (Figure 1, page 106). They are produced in the heart predominantly in response to increased left ventricular (LV) wall stress. As such, the majority of focus to date has been on their potential role in HF.

The circulating concentrations of both measurable forms of the peptide (BNP and NT-pro-BNP) have long been known to be elevated in patients with HF, be it acute or chronic, due to systolic dysfunction, or in the presence of preserved systolic function, and in its precursor form—asymptomatic LV dysfunction. They are elevated in proportion to the severity of the disease. Their concentrations rise with worsening New York Heart Association (NYHA) class and declining left ventricular ejection fraction (LVEF).
The evidence base is now such that B-type NPs are used in clinical practice as diagnostic tools for HF—in particular as rule-out tests in patients suspected on clinical grounds of having HF.8-10

All these properties would seem to point to B-type NPs being excellent surrogate markers for the presence of HF. However, the picture is a bit more complex. B-type NPs are not exclusive biomarkers of HF. While low concentrations rule HF out with a negative predictive value of around 98% to 99%, high concentrations do not necessarily diagnose HF. Concentrations are also raised in other forms of structural and functional heart disease, eg, acute coronary syndromes, myocardial infarction without systolic dysfunction, LV hypertrophy, and valve disease.11 They are also raised in patients with renal dysfunction where there is reduced clearance of the peptides.12 In addition, in obese HF patients, values can be lower than expected.13,14

**B-TYPE NATRIURETIC PEPTIDES AND PROGNOSIS IN HEART FAILURE**

Perhaps of greater interest to their putative role as a surrogate is the relationship between B-type NPs and outcome in HF.

There is now a wealth of data that B-type NPs are excellent prognostic markers in HF. Numerous studies confirm that they are independent arbiters of a poor prognosis in all grades of HF ranging from asymptomatic LV dysfunction through to NYHA class IV.15-20 Indeed they appear to be the best single prognostic markers we have to date, when we examine studies that have used multivariable models including established and novel markers of poor outcome including, NYHA class, LVEF, peak VO₂, serum sodium concentration, ORS duration, plasma catecholamine, and endothelin concentrations.18

In addition to their role in predicting all-cause and cardiovascular mortality in HF, they also seem to be effective in determining sudden cardiac death: in a study by Berger et al, an increased BNP concentration greater than the median was the only independent predictor of sudden death in 452 patients with LV systolic dysfunction.21 It would be tantalizing to think that we might be able to use B-type NPs in the future as surrogates to select patients for expensive device therapy in HF, eg, implantable cardioverter-defibrillators (ICDs) and cardiac resynchronization therapy (CRT and CRT-D) pacemakers.

Similarly, selection of patients for the scarce resource of cardiac transplantation in advanced HF is notoriously difficult. It usually relies on amalgamating a number of clinical variables to try to ascertain whether the patient’s prognosis merits the considerable risk of a 15% to 20% 1-year mortality that is associated with a transplant. It has been demonstrated that an NT-pro-BNP concentration greater than the median value at baseline was the single best predictor of mortality in patients referred for consideration of transplantation.22 How we use the information gained from this surrogate clinically is as yet unclear, ie, whether we take a single baseline value or a concentration that fails to fall on follow-up or whether we need to incorporate BNP/NT-pro-BNP concentrations into our clinical scoring models for assessing prognosis in HF remains to be determined.

Some information from studies in acute HF is unraveling the picture further about the usefulness of single or serial B-type NP measurements.

Cheng et al demonstrated in a study of 72 patients admitted to hospital with decompensated HF that the clinical end points of death or readmission to hospital with HF occurred in those whose BNP concentrations increased during the admission.23 There were no clinical end points in those whose BNP concentrations...
concentrations fell. However, a single predischarge BNP concentration was also an accurate determinant of readmission. Hence, in the patient with decompensated HF serial monitoring of BNP looking for a fall is helpful clinically.

Logeart et al, in an elegant study involving a derivation and validation cohort in patients with decompensated HF, reported that the predischarge BNP concentration was the best independent predictor of readmission, with a value of <300 pg/mL showing the lowest readmission rates. However, those patients with the greatest decrease in BNP had a better outcome than those with a more modest reduction (hazard ratio [HR], 0.18 [0.07-0.48]; P=0.001). Hence, in the decompensated situation serially measuring BNP and aiming for a discharge BNP <300 pg/mL seems important for discharge planning. Serial BNP testing has also been shown to be of more value in this situation that serial examination by Doppler echocardiography.

In chronic heart failure (CHF), fewer data are available on serial measurements. In the Valsartan–Heart Failure Trial (Val-HeFT), those patients with the greatest reduction in their BNP concentration (expressed as a change in quartile) had the lowest mortality over the course of the study. More recently, the Val-HeFT Group has published results using NT-pro-BNP from the placebo arm of the trial. A single determination of NT-pro-BNP showed higher prognostic discrimination than continuous changes of concentrations, expressed either as an absolute or a percentage change. However, in the Cox proportional hazards model stratification of patients into four categories according to NT-pro-BNP levels at two time points 4 months apart with respect to a threshold concentration provided prognostic information in patients with CHF beyond that of a single determination. Also, in chronic, but more advanced HF, it has been shown that NT-pro-BNP concentrations greater than the median on follow-up also predict a poor outcome as does an increase in NT-pro-BNP over 4 months of follow-up. It would appear that serially monitoring concentrations in CHF patients, therefore, seems to give additional information than merely looking at baseline values.

However, not all studies agree that using BNP concentrations as surrogate markers to make clinical decisions are useful. Lewin et al compared using BNP concentrations to serial weight changes to try and determine clinical deterioration in patients attending a HF clinic.
They found that neither was accurate enough to predict clinical deterioration. They pointed out that as yet we know little about the day-to-day, month-to-month variability of BNP in CHF patients to predict whether the changes we are looking for can be used. Wu et al recently showed that many short-term therapeutic studies of inpatients have largely resulted in statistically significant declines in BNP and NT-pro-BNP with clinical evidence of patient improvements.29 In contrast, however, many therapeutic studies involving long-term outpatient monitoring have produced changes in BNP/NT-pro-BNP that do not exceed the biological variance. More work clearly needs to be done here.

**B-TYPE NATRIURETIC PEPTIDE AND TITRATION OF THERAPY IN HEART FAILURE**

Another area of interest in B-type NPs as surrogates in HF concerns their use as a potential HbA1 or Biochemical Swan Ganz Catheter capable of monitoring progression of the disease and therefore prompting decisions of changes in therapy. To some extent the usefulness of this approach depends on what happens to B-type NP concentrations with the drug and device therapies we give for HF. Diuretics are known to reduce NP concentrations,30,31 whereas there are reports suggesting that digoxin increases their levels.32,33 However, it is the actions of the disease-modifying drugs that are perhaps the most interesting. There is good evidence that both angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) decrease B-type NP34,35 Tsuchimoto et al have reported in 37 patients with CHF that treatment with spironolactone for four months significantly reduces BNP concentration compared to placebo.36 The information regarding β-adrenoreceptor antagonists and B-type NP is a little more confusing to date. Data from the Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) study with metoprolol versus placebo treatment for 24 weeks reported a rise in BNP despite the expected improvement in LV function, reduction in mortality, and fall in angiotensin II and renin concentrations with metoprolol.37 However, in a nonrandomized Japanese study looking at 52 patients with CHF, again comparing metoprolol with placebo, both atrial natriuretic peptide (ANP) and BNP concentrations fell with the β-blocker.38 More recent work shows that they may increase BNP concentrations initially, but chronically they seem to reduce them—this fits with these agents’ effects on long-term reverse remodeling.39

Hence, at the moment, two speculative schools of thought exist. The first presume that initially the β-adrenoreceptor antagonists increase B-type NP due to their negatively inotropic and chronotropic properties and that as the beneficial effect of these drugs on LV function emerge the peptide concentrations fall. The second group proposes that the improvement seen with these drugs could be explained, at least in part, by their ability to increase NP levels. Irrespective of the effect of β-blockade, evidence is now emerging suggesting that when we optimize therapy in patients with HF, be that by increasing ACE inhibitor, adding spironolactone, or uptitrating β-adrenoreceptor antagonists—which is, after all what we do when dealing clinically with HF patients—that B-type NP concentrations fall.40

CRT also reduces BNP concentrations.41 The real question arising from these observations is, however, do these reductions in B-type NP concentrations matter? The answer is probably yes as we know, as stated above, that patients whose BNP concentrations fall during an admission with HF and chronically have a better outlook that those patients where the levels fail to fall.

However, randomized studies of B-type NP–driven care versus usual care are scarce. Murdoch et al randomized small group of 20 patients attending a HF clinic to usual care or optimization of HF drugs according to BNP concentrations where the BNP target was to be within the normal range. The study showed a greater suppression of markers of the renin-angiotensin-aldosterone system in those receiving BNP-driven care.42

Richard’s group published a small study of 69 patients attending a HF clinic. They were randomized to care according to their aminoterminal portion of BNP (N-BNP) concentration/usual care. Those allocated to N-BNP driven care had a significantly lower incidence of death or readmission to hospital at 6 months, (P=0.034), suggesting that this approach may give superior patient outcomes. Subsequently, the Systolic heart Failure Treatment Supported by BNP (STARS-BNP) study reported beneficial effects in those randomized to BNP driven care in 220 outpatients with CHF due to systolic dysfunction.44 There was a statistically significant absolute reduction of 28% in the combined primary end point of HF-related death or hospitalization (P<0.001) (Figure 2).

In summary, to date, observational evidence shows that monitoring with B-type NP as a surrogate marker can help with discharge planning and risk stratification for intensification of HF therapy. However, we await more randomized studies such
as the Pro-BNP Evaluation Study to confirm the clinical utility of this approach. We also clearly need more data on day-to-day variability of B-type NP in CHF.

As regards using B-type NP for titration of HF therapy, two recent larger studies been recently published. BATTLESCARRED\(^4\) suggested improved outcome with BNP-guided therapy, but only in patients younger than 75 years. In TIME-CHF\(^4\), in patients aged 60 years or older (mean age approximately 77 years), there was no statistically significant difference in the primary end point of 18-month survival free of all-cause hospitalization. As of now we can say that B-type NP in HF does not yet have the status of cholesterol in coronary heart disease as a target for treatment in itself.

**B-TYPE NATRIURETIC PEPTIDE AND HEART FAILURE TRIALS**

The evidence that is of most relevance in promoting B-type NP as a surrogate end point in HF is that available from the landmark HF treatment trials to try determine whether these peptides track with the main mortality and morbidity end points and in addition whether their association with the randomized therapy being tested goes in the same direction as the result, be it positive or negative. Evidence from the major trials is sometimes lacking as B-type NP was first measured in a clinical trial in HF in the Australia–New Zealand (ANZ) trial of carvedilol that published in 1997.\(^4\) Here only baseline values were measured. The study demonstrated that in patients with established ischemic LV dysfunction, plasma N-terminal pro-B-type natriuretic peptide (N-BNP) was an independent predictor of mortality and HF and that carvedilol reduced mortality and HF in patients with higher pretreatment plasma N-BNP concentrations. More recent trials have measured serial concentrations and have therefore been able to speculate on B-type NP as a surrogate end point.

**Chronic systolic heart failure trials**

- **ACE inhibition.** The major ACE inhibitor trials predate B-type NP measurements. More recently, they were measured in the Carvedilol ACE inhibitor Remodeling Mild congestive heart failure Evaluation (CARMEN) trial, where NT-pro-BNP and BNP concentrations fell with enalapril in 6 months of follow-up.\(^4\) Extrapolating these results to the undoubted efficacy of ACE inhibitor in CHF patients with systolic dysfunction, this is a “pro” for B-type NP as a surrogate.

- **β-Adrenoceptor antagonists.** Bearing in mind the controversies about B-type NP and β-blocker therapy in HF, the trial results are remarkably consistent. In the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) study, which demonstrated that carvedilol reduced mortality in advanced CHF, BNP concentrations also fell in those assigned to carvedilol.\(^4\) Interestingly, in the Beta-

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### Figure 2. Effects of BNP-guided care (green) on event-free survival in chronic heart failure.

3 months and 6 months ($P=0.004$ and $P=0.05$, respectively) in the group assigned to spironolactone; another result in the correct direction for BNP as a surrogate.  

- **Angiotensin receptor blockers.** In the Val-HeFT trial, BNP rose over time in the placebo group. Valsartan caused a sustained reduction in BNP. This effect of valsartan is consistent with the clinical benefits reported, i.e., a reduction in the combined composite primary end point of morbidity and mortality by 13.3%.  

Data from other ARB studies, particularly the Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity (CHARM) program, are awaited as they still have to report their neurohormonal substudies.

- **Hydralazine plus nitrate.** The African-American–Heart Failure Trial (A-HeFT) examined the effects of combination therapy with hydralazine and isosorbide dinitrate compared with placebo in African-American patients with CHF due to systolic dysfunction. Patients were on standard optimal medication for HF. BNP concentrations fell significantly in treatment group (39 pg/mL versus 8 pg/mL in the placebo arm; $P=0.05$).  

Again this is consistent with the improvement in the primary end point, which was a composite score including all-cause mortality, first HF hospitalization, and change in quality of life ($P=0.01$). There was also a reduction in all-cause mortality ($P=0.02$).

In these large randomized trials in CHF there does seem to be remarkable consistency between B-type NP measurements and the main end point.

**Studies in acute HF**

Investigators have only really embarked upon large randomized trials in acute HF relatively recently. However, some data on B-type NP are emerging from these and producing different though not necessarily inconsistent results.

In the Survival of Patients With Acute Heart Failure in Need of Intravenous Inotropic Support (SURVIVE) trial, which compared the effects of levosimendan versus dobutamine in 1327 patients with acute decompensated HF and low ejection fraction requiring inotropic therapy, there was no difference in all-cause mortality at 180 days. However, BNP concentrations fell significantly in the levosimendan-treated group. BNP was only measured during the in-hospital infusion phase of the trial, but we can say that the transient reduction did not go in the same direction as the 180-day outcome measure. In contrast, in the recent Hemodynamic, Echocardiographic, and Neurohormonal Effects of Istaroxime in Acute Heart Failure Syndromes (HORIZON-HF) study looking at the effects of the new inotrope istaroxime, in patients with decompenated HF, there were significant changes in the hemodynamic end points in favor of istaroxime, but no change in BNP concentrations.

In the Randomized Intravenous TeZosentan (RITZ) trial of a low dose of the endothelin antagonist tezosentan in patients admitted with acute HF, tezosentan doses of 1 to 25 mg/h were efficacious in improving the hemodynamics and reduc-

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**Figure 3. The effects of CRT on NT-pro-BNP concentrations in the CARE-HF trial.**

Abbreviations: CARE-HF, Cardiac Resynchronization therapy in Heart Failure trial; CRT, cardiac resynchronization therapy; NT-pro-BNP, N-terminal fragment of pro-BNP.

ing BNP, showing a move of both end points in the same direction. Overall, to date, we could conclude that for short-time inotropic studies or studies of other agents in acute HF, B-type NP does not appear to be a reliable surrogate marker.

**Small proof-of-concept and pilot studies**

Several smaller trials of newer therapeutic strategies are already using changes in B-type NPs as exploratory end points to build a more robust body of evidence prior to embarking on larger definitive outcome studies. Such trials, eg, those using erythropoietins, seem to show reductions in B-type NPs in HF patients with concomitant improvements in clinical status.

**CONCLUSIONS**

The evidence to date points to B-type NP having the potential to be a useful surrogate end point in HF trials. B-type NPs are raised in HF syndromes, elevated concentrations and levels that fail to fall during therapy portend a poor prognosis; and titration of known efficacious drugs according to their concentrations in plasma seems to be beneficial. In large randomized trials of interventions in chronic systolic HF, B-type NP changes seem to be in the same direction as the harder end points.

However, before we can recommend using B-type NP as surrogate primary end point for clinical trials across the HF spectrum, we will need to see much more data emerging from the more recent large randomized HF trials. This should provide us with more information on how B-type NP fares as an end point in trials of HF with preserved LVEF and in acute HF syndromes in addition to those already seen in CHF due to systolic dysfunction.

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Effects of darbepoetin alpha on right and left ventricular systolic and diastolic function in anemic patients with chronic heart failure secondary to ischemic or idiopathic dilated cardiomyopathy.

Effects of beta-erythropoietin treatment on left ventricular remodeling, systolic function, and B-type natriuretic peptide levels in patients with the cardiorenal anemia syndrome.
Cardiovascular disease still accounts for most of the morbidity and mortality in Western countries. The underlying cause of most forms of cardiovascular disease, specifically myocardial infarction and stroke, is atherosclerosis. Atherosclerosis develops over decades and may lead to vascular occlusion with devastating clinical consequences. The process is initiated by endothelial dysfunction, followed by intimal thickening with deposition of lipoproteins, and invasion of macrophages and other white blood cells. Atherosclerosis leads to angina pectoris; plaque rupture or endothelial erosion leads to platelet activation, initiation of the coagulation cascade, thrombus formation, and eventually vascular occlusion. The latter events account for most of the morbidity in stroke and acute coronary syndromes.

Keywords: heart failure; atherosclerosis; cardiovascular disease; surrogate end point; endothelial dysfunction

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such as acetylcholine (Figure 1). The healthy endothelium is placed in an anatomically strategic position between the circulating blood and vascular smooth muscle cells of the media, and is able to respond appropriately to physical and chemical signals by the production of a wide range of factors that regulate vascular tone, cellular adhesion, thrombosis, vascular inflammation, and hypertrophy (Figure 1). Importantly, healthy endothelium, via the release of NO, inhibits platelet and leukocyte adhesion to the vascular surface, while, through the release of tissue plasminogen activator as well as plasminogen activator inhibitor-1 and tissue factor, it maintains a balance of profibrinolytic and antithrombotic activity (Figure 2).

**Figure 1**: Endothelium-derived vasoactive substances.

NO is released from endothelial cells in response to shear stress and to activation of a variety of receptors. NO inhibits thrombocyte aggregation and leukocyte adhesion, and exerts vasodilating and antiproliferative effects on smooth muscle cells. Through activation of the ET1-receptor, ET1 leads to vasoconstriction and cell proliferation; in contrast, activation of the ET2-receptor results in vasodilation (via release of NO and prostacyclin).

**Abbreviations**: AI, angiotensin I; AII, angiotensin II; ACE, angiotensin-converting enzyme; Ach, acetylcholine; AT1, angiotensin 1 receptor; BK, bradykinin; cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; COX, cyclooxygenase; ECE, endothelin-converting enzyme; EDBH, endothelin-derived hyperpolarizing factor; ET1, endothelin A receptor; ET2, endothelin B receptor; ET-1, endothelin-1; 5-HT, 5-hydroxytryptamine (serotonin); L-Arg, L-arginine; M, muscarinic receptor; NAD(P)H Ox, phosphorylated nicotinamide adenine dinucleotide oxidase; NO, nitric oxide; NOS, nitric oxide synthase; PGH2, prostaglandin H2; PGI2, prostacyclin; S, serotoninergic receptor; T, thromboxane receptor; Thr, thrombin; TGF-β1, transforming growth factor-β1; TX, thromboxane; TXA2, thromboxane A2.


**Figure 2**: The healthy endothelium not only mediates endothelium-dependent vasodilation, but also actively suppresses thrombosis, vascular inflammation, and hypertrophy. Nitric oxide is a particularly important mediator of both endothelium-dependent vasodilation and anti-inflammatory and antithrombotic effects of the endothelium, and endothelium-dependent vasodilation is therefore thought to represent a “read-out” of other important functions of the endothelium.

The endothelium is constantly exposed to various risk factors in the circulating blood such as pressure, shear stress, lipoproteins, glucose, and others. Over the last decades it has been recognized that common conditions predisposing to atherosclerosis, such as hypertension, hypercholesterolemia, diabetes, and smoking are associated with endothelial dysfunction, leading to a proinflammatory and prothrombotic phenotype of the endothelium. Our current understanding of the pathobiology of atherosclerosis suggests that endothelial dysfunction plays a pivotal role in the development and progression of atherosclerosis and its clinical complications.

**Endothelial dysfunction and aging**

Celermaier and coworkers were one of the first groups who demonstrated that aging was associated with progressive endothelial dysfunction in healthy elderly subjects free of risk factors or vascular disease. They studied the response of the brachial artery to increased flow (so-called flow-dependent dilation) after prolonged occlusion of the vessel by a blood pressure cuff, and the response to the endothelium-independent vasodilator glyceryl trinitrate. In the 238 subjects studied, they found an age-related development of endothelial dysfunction both in men and in women. Interestingly, endothelial dysfunction appeared to occur earlier in males than in females. Women appeared somehow protected from vascular aging until around the time of the menopause. After the onset of menopause an increase in endothelial dysfunction was observed.

**Endothelial dysfunction and hypertension**

Alterations in endothelial function are detectable in experimental and human hypertension, both in the forearm circulation, as well as in the coronary vascular bed (Figure 3). In human hypertension, the mechanisms appear to be different at various stages of the hypertensive process, and somehow endothelial dysfunction precedes the development of hypertension as normoten-

![Figure 3. Vasodilation in response to acetylcholine infused in the forearm microcirculation. Patients with essential hypertension (light green circles); normotensive subjects with no family history of hypertension (dark green circles). The vasodilation, as represented by forearm blood flow (FBF) measured with strain-gauge plethysmography, was significantly blunted in hypertensive patients as compared to normotensives. The FBF response to sodium nitroprusside, a nonendothelium-dependent vasodilator, was similar between the 2 groups. *p<0.01 hypertensive vs normotensive subjects. Modified after reference 17: Taddei et al. Hypertension. 1997;29(3):736-743. © 1997, American Heart Association, Inc.](image)

Endothelial dysfunction and hypercholesterolemia

Elevated low-density lipoprotein (LDL) cholesterol, in hypercholesterolemia, is a known risk factor for the development of atherosclerotic vascular disease and causes endothelial dysfunction. In the early phase of atherosclerosis, LDL gets trapped in the subendothelial space and undergoes oxidation (Figure 4). Oxidized LDL has several biologi-
calcium effects, it is proinflammatory, it inhibits endothelial nitric oxide synthase (eNOS), it promotes vaso- 
constriction and adhesion, stimulates cytokines such as interleukin-1 (IL-1) and increases platelet aggrega-
tion. The release of cytokines attracts monocytes to the vascular endothe-
lium. After their migration into subendothelial compartments, monocytes differentiate under the influence of monocyte colony stimu-
ulating factor (M-CSF) into macrophages.28 These macrophages take 
up modified LDL by their scavenger receptor and in turn differentiate 
into foam cells (Figure 4). Accumula-
tion of these LDL-laden macrophages 
leads to the formation of “fatty streaks,” the earliest manifesta-
tion of atherosclerosis, which later 
turn into fibrous plaques. In con-
trast to LDL cholesterol, high-den-
sity lipoprotein (HDL) cholesterol 
exerts a protective effect and in-
versely correlates with morbidity 
and mortality. HDL is an impor-
tant antioxidant. Consequently, intravenous infusion of HDL restores the 
impaired flow-mediated dilation (FMD) by improving NO bioavail-
ability in the brachial artery of pa-
tients with endothelial dysfunction 
due to hypercholesterolemia 
(Figure 5, page 118).29

**Endothelial dysfunction and diabetes**

Cardiovascular disease is the major complication of diabetes. Experi-
mental and clinical studies have shown that diabetes is associated 
with endothelial dysfunction. Both non–insulin-dependent and insulin-
dependent diabetes mellitus are 
associated with impaired endothelial–dependent vasodilation even 
in patients without other risk factors like hypertension or hypercholes-
terolemia.30-32 Although abnormalities leading to endothelial dysfunc-
tion may differ between type 1 and 
type 2 diabetes, decreased NO 
bioactivity, reflecting a defective 
L-arginine/nitric oxide pathway, may 
be, in part, responsible for the in-
creased cardiovascular risk associat-
ed with type 1 and 2 diabetes.

**ASSESSMENT OF ENDOTHELIAL DYSFUNCTION**

Several years after Furchgott and 
Zawadzki’s seminal demonstration 
of endothelium-dependent relax-
ations to acetylcholine in the isolat-
ed rabbit aorta,1 similar responses
could be demonstrated in the human forearm. In certain endothelium-denuded vessels such as the human coronary artery, acetylcholine causes vasoconstriction due to a direct effect on vascular smooth muscle cells. In line with this observation, intracoronary infusion of acetylcholine in the catheter laboratory induces small increases in epicardial coronary artery diameter in patients without coronary artery disease and no risk factors, but profound paradoxical vasoconstriction in patients with coronary disease. In later studies, Quyyumi et al confirmed that the impaired response to acetylcholine in patients with coronary disease or cardiovascular (CV) risk factors was largely due to reduced coronary availability of endothelium-derived NO. The direct assessment of coronary endothelial function—due to its invasive nature—is restricted, limited to patients with advanced disease, and repeated testing during serial follow-up is difficult and costly.

**Figure 5. Forearm arterial vasodilator response.**

A. Forearm blood flow during intra-arterial infusion of acetylcholine. Endothelium-dependent vasodilation to acetylcholine is impaired in hypercholesterolemic compared with normocholesterolemic controls (P<0.0001), whereas there is no difference in the vasodilator response to sodium nitroprusside, an endothelium-independent vasodilator. In hypercholesterolemic subjects, there is a significant improvement in endothelium-dependent vasodilatation to acetylcholine after administration of reconstituted HDL. B. Improvement in endothelium-dependent vasodilation to acetylcholine induced by reconstituted HDL is prevented by intra-arterial coinfusion of L-NMMA, an inhibitor of NO synthesis, identifying improved NO bioavailability as the responsible mechanisms for the improvement in endothelial function. C. Flow-mediated dilation of the brachial artery in hypercholesterolemic subjects before and after intravenous infusion of reconstituted HDL. There is a significant improvement in endothelium-dependent vasodilatation of the brachial artery, which does not depend on acetylcholine or its receptors.

**Figure 6. Flow-mediated dilation (FMD) of the brachial artery.**

A. Ultrasound probe held in stereotactic clamp with micrometer adjustment. B. Continuous measurement of brachial artery diameter before, during, and after inflation and release of sphygmomanometer cuff on forearm. The analog video signal is acquired with a video processing system that computes the artery diameter in real-time. FMD Studio, A system for Real-Time Measurement, Institute of Clinical Physiology, Pisa, Italy, see refs 38 and 39.
Because endothelial dysfunction is a systemic process, a less invasive approach using venous occlusion plethysmography has been adopted that utilizes the same principles of local (ie, intrabrachial) infusion of pharmacological probes and measurement of changes in tone of forearm resistance vessels. This technique provides an opportunity to evaluate endothelial pathophysiology during the preclinical stage of the disease. Indeed, using appropriate agonists and antagonists, dose-response curves to acetylcholine, sodium nitroprusside, L-NMMA and vasoconstrictor hormones can be constructed. Venous occlusion plethysmography has been widely used, but it is an invasive technique that requires arterial cannulation. This limits its repeatability, and prohibits its use in larger studies.

In 1992, Celermajer and coworkers introduced an ultrasound-based test to assess conduit artery vascular function in the systemic circulation (Figure 6). With this method, brachial artery diameter is measured before and after an increase in shear stress arising from the circulating blood that is induced by reactive hyperemia (FMD). A sphygmomanometer cuff is placed on the forearm distal to the brachial artery and inflated up to 200 mm Hg and then subsequently released 4 to 5 minutes later. As described by the German physiologist Schretzenmaier at the beginning of the 20th century, FMD of the brachial or radial artery occurs predominantly as a result of the shear stress–induced endothelial release of NO (Figure 7).

As in the coronary circulation, the response of the brachial or radial artery can be compared to the endothelium-independent vasodilator response to sublingual nitroglycerine. Measurements of FMD by ultrasound are technically demanding, but can be standardized to yield reproducible results that correlate with coronary vascular endothelial function and strain-gauge plethysmography. Modern software development has allowed for continuous assessment of arterial diameter and blood flow throughout the whole protocol by use of accurate edge detection algorithms that can be manually edited. It is important to note that variations in technique, such as the position of the occluding cuff and duration of inflation, may produce results that are less representative of local NO activity. Brachial artery FMD has been widely studied in clinical research as it enables serial evaluation of young subjects, including children. It also allows the assessment of the effects of lifestyle and pharmacological interventions on endothelial biology at an early preclinical stage, when the disease process is most likely still reversible. In recent years, several other noninvasive techniques for the characterization of vascular function have been proposed, including pulse wave analysis, pulse wave velocity measurement, and pulse amplitude tonometry. Interestingly, in 2000 subjects of the Framingham Third Generation Cohort, endothelial vasomotor function testing before and after reactive hyperemia in the fingertips using pulse amplitude re-

**Figure 7. Changes in radial artery flow and diameter.**

Bar graphs showing radial artery flow (mL/min) and radial artery diameter (mm) measured at baseline (Base) and during reactive hyperemia before and after infusion of NG-monomethyl-L-arginine (L-NMMA). All results are the mean±SEM of eight subjects. **P<0.01 vs Base; †P<0.05 and ††P<0.01 vs corresponding control value.


Further work is required to validate the potential role of RH-PAT and other emerging noninvasive tests of vasomotor function as independent predictors of cardiovascular risk and later clinical events. In particular, comparison with other tests—like ultrasound FMD and venous occlusion plethysmography—known to have prognostic value in the context of cardiovascular disease (see below), needs further investigation.
ENDOTHELIAL DYSFUNCTION AND MAJOR CARDIOVASCULAR EVENTS

Over the last years, several studies, utilizing different tests of vasomotor function, have established endothelium-dependent vasomotor function as an independent predictor of the long-term risk of major cardiovascular events, including sudden cardiac death, myocardial infarction, and stroke. Of note, in 2005, Lerman and Zeiher published a multivariate meta-analysis of 10 studies involving a total of 2500 subjects, which analyzed the relationship between coronary or peripheral endothelial dysfunction and cardiovascular events.46 Their findings strongly supported the notion that endothelial dysfunction is independently associated with the risk of major cardiovascular events, even after adjustment for presence of coronary artery disease and/or cardiovascular risk factors (Figures 8 and 9).46,47

The prognostic value of endothelial dysfunction was not only investigated in patients with known atherosclerosis, but also in those with risk factors. In postmenopausal women with newly diagnosed hypertension, Modena and coworkers examined FMD noninvasively in the brachial artery.48 Patients with persistent endothelial dysfunction after 6 months despite appropriate blood pressure-lowering therapy had an increased risk of nonfatal cardiovascular events over the next 5 years. Although treatment was not standardized, the type of antihypertensive therapy or the degree of blood pressure lowering did not explain the difference in outcome. This study strongly suggests a possible value of endothelial function as a screening test for the primary prevention of cardiovascular disease and for assessing therapy.

EFFECT OF CARDIOVASCULAR DRUGS ON ENDOTHELIAL DYSFUNCTION

Statins

Statins are well established in the secondary prevention of cardiovascular disease, indeed, these drugs improve the prognosis of patients with atherosclerotic vascular disease even in the presence of so-called normal cholesterol plasma levels.49,50 Of note, statins upregulate eNOS expression, leading to improved NO bioavailability, improved endothelial function, and reduced transient myocardial ischemia, suggesting that these vascular biological effects of HMG-coenzyme A reductase inhibitors may importantly contribute to the clinical benefits.51-54 Indeed, in the forearm circulation of patients with hypercholesterolemia, statins improve FMD within weeks of treatment, an effect that is lost after stopping the treatment.55 In the coronary circulation of patients with coronary artery disease, treatment with either simvastatin (Coronary Artery Reactivity After Treatment with Simvastatin [CARATS] trial)56 or cerivastatin (Evaluation of Nifedipine and Cerivastatin On Recovery of coronary Endothelial function [ENCORE I] trial)57 for 6 months failed to improve the paradoxical vasoconstriction of epicardial coronary arteries to acetylcholine. Although smaller studies suggested a rapid benefit of statin treatment on coronary vasomotion,58 larger trials showed that it probably takes more than 6 months to improve coronary vasomotion, an interpretation in line with the observation that in clinical trials Kaplan-Meier survival curves of placebo- and statin-treated patients diverge only after 1 to 2 years.

Although a first attempt to raise LDL with the cholesterol ester transport protein (CETP) inhibitor torcetrapib was disappointing, HDL remains a potential target for the prevention of vascular disease. Indeed, low HDL is a principal risk factor for the development of premature coronary
artery disease, and overall the influence of statin therapy on HDL cholesterol levels is rather modest. Of note, intravenous infusion of reconstituted HDL in patients with hypercholesterolemia rapidly improves endothelial function in the forearm circulation, both when assessed with intra-arterial acetycholine infusion as well as FMD. Interestingly, HDL has profound anti-inflammatory effects.\(^5\) Furthermore, in a small pilot study, Hermann et al\(^6\) showed that dalcetrapib, another CETP inhibitor (which in contrast to torcetrapib does not increase blood pressure) improved FMD in patients with low HDL. A large study (DAL-Vessel-Trial) involving 500 patients with coronary artery disease or at high risk using this novel compound is currently ongoing.

**Angiotensin-converting enzyme (ACE) inhibitors**

ACE inhibitors not only prevent the formation of angiotensin II, but also inhibit the breakdown of bradykinin, a stimulator of NO release. Moreover, their antioxidant properties improve NO bioavailability, and thereby endothelial function, as assessed in the forearm macro- and microcirculation\(^6\) as well as in the coronary circulation.\(^6\) They furthermore inhibit the endothelial production of angiotensin II (All) and endothelin 1 (ET\(_1\)), two potent vasoconstrictors (Figure 10, page 122, and Table 1, page 123).\(^6\) Hence, ACE inhibitors have important effects on endothelial function. In the Trial on Reversing Endothelial Dysfunction (TREND), involving patients with coronary artery disease with normal blood pressure, near-normal lipid profile, and no evidence of heart failure, ACE inhibition with quinapril markedly improved endothelial dysfunction, as assessed by intracoronary infusion of acetycholine within 6 months.\(^6\) Besides ACE inhibition per se, certain compound-specific pharmacological features may be important for such effects, for example, in patients with coronary artery disease, only quinapril, but not enalapril, was associated with a significant improvement in FMD of the brachial artery.\(^6\) Further to their vascular effects, improved NO bioavailability during ACE inhibitionalso affects platelet function, and inhibitors of the renin-angiotensin-aldosterone system indeed inhibit platelet aggregation in vitro. Overall, the aforementioned effects may at least in part be responsible for the clinical benefits observed in patients with atherosclerosis even in the absence of hypertension (Heart Outcomes Prevention Evaluation [HOPE] trial).\(^6\)

More recently, the PERIndopril Thrombosis, Inflammation, Endothelial dysfunction, and Neurohormonal activation Trial (PERTINENT)\(^6\) has provided further insights into the mechanism of morbidity and mortality benefits associated with perindopril in the...
EUROPA trial (European trial on reduction Of cardiac events with Perindopril in stable Coronary Artery disease). It was found that perindopril restored the balance between angiotensin II and bradykinin in favor of bradykinin, improved endothelial function, and decreased the endothelial cell apoptosis rate.

Angiotensin receptor blockers (ARBs)

ARBs also have pronounced effects on vascular function. Candesartan reduces vasoconstriction to endogenous ET-1 and improves tonic NO release in the forearm of hypertensive patients. Treatment of hypertensive patients with irbesartan enhanced both endothelium-dependent and -independent vascular vasodilation responses. Furthermore, some ARBs may reduce thromboxane A2-dependent platelet activation, possibly independent of the angiotensin II receptor. In head-to-head comparison, angiotensin-II–receptor blockade appears to have stronger anti-inflammatory and antiaggregatory effects compared with ACE inhibition; indeed, both ACE inhibition (with enalapril) and angiotensin-II–receptor blockade (with irbesartan) reduce serum metalloprotease-9 protein levels as well as enzyme activity to a similar extent, while in patients with coronary artery disease only irbesartan also reduced high-sensitivity C-reactive protein, interleukin-6, and platelet aggregation. Interestingly, the combination of an ACE-inhibitor (ramipril) and an ARB (candesartan) has a synergistic effect in improving endothelial function (as measured by flow-mediated vasodilation).

Calcium channel blockers (CCBs)

Several CCBs have been successfully used to improve endothelial function in patients with hypertension. Indeed, long-term treatment with nifedipine has been shown to improve endothelium-dependent vasodilation to acetylcholine in the forearm circulation of hypertensive patients.
Could endothelial dysfunction be a surrogate end point for CAD? - Wolfram and others

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Table 1. Changes in epicardial luminal area.

Abbreviations: ACE: angiotensin converting enzyme; ARB: angiotensin Receptor Blocker; Ca: calcium; ACh: acetylcholine; MCh: metacholine; LNMMA: L-N-monomethylarginine; FMD: flow-mediated dilation.

*This effect was paralleled by an enhanced endothelium-independent vasodilatation to sodium nitroprusside.

Modified after reference 63: Sudano et al. Hot Topics in Cardiology. 2009 (No. 15).
patients, while the response to sodium nitroprusside remained unaffected. In contrast, ACE inhibition improved the response to bradykinin, but not acetylcholine in this patient population. Furthermore, chronic treatment with nifedipine (even though the drug was stopped before testing) blunted the vasoconstriction to endothelin-1. Most interestingly, in hypercholesterolemia, the CCB nifedipine improves endothelial function independent of its effect on blood-pressure or plasma lipids, most likely by a reduction in NO degradation. Indeed, oral treatment with dihydropyridine calcium antagonists reduces oxidative stress, thereby improving bioavailability of NO in the forearm circulation. Many molecules belonging to this pharmacological class improve endothelial function in humans (Table I). This effect is likely to be specific to dihydropyridine calcium antagonists, while nondihydropyridine calcium antagonists, eg, verapamil, have no effect on endothelial function (Table I).

In patients with coronary artery disease, CCBs were extensively investigated as to their effects on endothelial function and plaque size and progression. Initially, the International Nifedipine Trial on Antiatherosclerotic Therapy (INTACT) suggested that nifedipine suppresses disease progression (as demonstrated by the appearance of new lesions by quantitative coronary arteriography). In ENCORE I, nifedipine markedly suppressed the paradoxical vasoconstriction to acetylcholine in epicardial coronary arteries of patients undergoing percutaneous coronary intervention in another than the target artery. As this effect was noted even after the drug had been stopped for several days and persisted up to 18 month as demonstrated in ENCORE II, the calcium antagonist appears to consistently improve coronary endothelial function. The effect of dihydropyridine calcium antagonists on endothelial function are summarized in (Figure 11). These effects may explain the anti-ischemic properties of this class of drugs as demonstrated in the A Coronary disease Trial Investigating Outcome with Nifedipine GITS (ACTION).

**β-Blockers**

In contrast to the previously discussed drugs, most β-blockers do not improve endothelial function. Indeed, hypertensive patients treated with atenolol for 1 and 3 years, as well as 5 months with metoprolol had no improvement in endothelial function (Table I). In contrast, new-generation β-blockers, such as nebivolol and carvedilol, seem to improve this response (Table I and Figure 12). As far as nebivolol is concerned, its NO releasing properties may explain this difference as it was demonstrated in patients with hypertension (Table I). Interestingly, even in healthy subjects, infusion of nebivolol improves endothelial function. Similar effects were shown with carvedilol, a selective β₁- and α₁-antagonist with marked antioxidant properties, not only in hypertensives, but also in patients with
diabetes or coronary artery disease (Table 1). This is of particular interest since carvedilol was superior to metoprolol in the Carvedilol Or Metoprolol European Trial (COMET) in preventing death.

To conclude, many drugs with proven efficacy in the prevention of major cardiovascular events have also been shown to improve endothelial function in the peripheral and/or coronary circulation. However, the results of some studies have to be interpreted with caution. Indeed, in some cases promising data from initial studies could not be subsequently confirmed. Several reasons may explain these discrepancies.

Besides type 1 errors, patient numbers and consequently statistical power of many studies were not sufficient. Furthermore, the sophisticated tests to assess endothelial function require extensive training and certification of the operators involved. Better standardization to minimize the effect of environmental or physiological influences, such as exercise, eating, caffeine ingestion, and variations in temperature is also needed.

Thus there is a need of further large prospective studies with highly trained investigators to ensure appropriate data quality to evaluate the effects of earlier and newer drugs on the vessel wall, and the endothelium in particular. Such trials should be part of a comprehensive program that would also include large morbidity and mortality trials to assess whether the beneficial effect on endothelial function of a given drug is truly followed by improved prognosis in patients with cardiovascular disease.

**SUMMARY**

Numerous clinical studies have documented the presence of endothelial dysfunction at all clinical stages of atherosclerotic vascular disease and shown that the presence and the degree of endothelial dysfunction are independently associated with the risk of major cardiovascular events, even after adjustment for the presence of coronary artery disease and/or cardiovascular risk factors. Assessment of endothelial function as an integrative marker reflecting the effects of risk factors on the vessel wall has become a highly valuable clinical research tool in cardiovascular disease. However, whether it can be used routinely in daily clinical practice on top of careful evaluation of classic risk factors to improve cardiovascular risk prediction, stratify individual cardiovascular risk, and document the effect of therapeutic interventions on vascular function requires further investigation through large prospective studies. The evaluation of emerging simpler and more easily applicable noninvasive technologies also needs further investigation and validation.
Could endothelial dysfunction be a surrogate end point for CAD? - Wolfram and others

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Can there be any surrogate for safety?

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Clinical outcomes–focused randomized clinical trials are the current gold standard for evidence-based medicine. However, it is impractical and not feasible to attempt to answer all questions with large clinical outcomes trials. Surrogate markers are often utilized as alternative measures in smaller and shorter-duration trials. However, they are not always a reliable barometer of intervention-induced alterations in prognosis. This manuscript highlights several prominent instances where the clinical effects produced by a therapy were not adequately predicted by changes in an allegedly reliable and important surrogate. In addition, trials targeting only surrogate markers do not have sufficient exposure to unmask potential safety issues of the intervention. In highlighting the limitations of surrogate-marker–based trials, we emphasize the need for more definitive clinical outcomes trials to better guide clinical practice.

Key words: clinical trial; evidence-based medicine; end point; heart failure; safety; therapy; prognosis

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Dialogues Cardiovasc Med. 2010;15:130-139

The randomized controlled clinical trial (RCT) is the current foundation for obtaining vital information upon which to base clinical decisions. The RCT is, however, a relatively new tool in our armamentarium of clinical investigation. The processes of randomization, blinding, and when appropriate, use of placebo, reduce biases and provide a framework for valid statistical comparisons. Modern RCTs assessing risks for clinical events were first used in infectious diseases. The 1948 trial which provided proof that in patients with tuberculosis those randomly assigned to therapy with streptomycin had a lower mortality at 6 months (7% of streptomycin patients and 27% of the bed rest alone group) is historically the first RCT demonstrating a survival benefit of a therapy.1

In our view, the roots of clinical outcomes RCTs in cardiovascular medicine can be traced to the original Veterans Association (VA) Cooperative Study Group on Antihypertensive Agents.2 Under the leadership of the late Dr Edward Freis, this still active clinical trials organization tested the hypothesis that the adverse association between elevated blood pressure and cardiovascular outcomes highlighted by the pioneering epidemiologic work from the Framingham study3 could be favorably modified by reducing blood pressure with pharmacologic therapies. The Veterans investigators established in patients with severe diastolic hypertension that, compared with placebo, those randomized to receive the combination of three antihypertensive agents (hydralazine, hydrochlorothiazide, and reserpine) had a lower incidence of the composite of death and non-fatal cardiovascular outcomes.2 This historic paradigm shifting trial provided the rationale for pharmacologic use of antihypertensive therapies in hypertension to reduce adverse cardiovascular outcomes, not just blood pressure. By today’s standards, the first VA trial, with relatively few events and a composite of predominantly nonfatal outcomes, would not be considered as definitive. However, this demonstrated the importance of conducting RCTs to impact cardiovascular prognosis and serves as the foundation for RCTs testing clinical outcomes.

In the ensuing 50 years, the totality of the evidence for the importance of pharmacologic blood pressure lowering in hypertension has been based on the compilation of RCTs.
that demonstrate major reductions in risk for cardiovascular events. In general, the greater the extent of blood pressure lowering achieved, the lower the risk for subsequent cardiovascular events. It is important to note that these large placebo controlled clinical outcome RCTs also generate quantitative data regarding the adverse experiences that can be attributed to these pharmacologic therapies. This aspect of the large clinical outcome assessing RCTs should not be undervalued, as therapeutic decisions are based on the best available estimate of both potential benefits as well as the safety and tolerability of the intervention.

**END POINTS IN RCTs**

The medical community is familiar with the components of well-designed RCTs. Although many emphasize the inclusion and exclusion criteria, sample size, event rates, and duration, the fundamental reason to conduct a RCT is to determine whether the primary objective is altered by the intervention. By definition, the primary objective is the end point upon which the statistical framework for accepting or rejecting the hypothesis is based. As is covered by Anand and Florea in this issue of *Dialogues in Cardiovascular Medicine*, few would argue that trials comparing rates of death or all-cause mortality are testing the most definitive, unbiased, and irrefutable of all end points. In cardiovascular medicine, we have been fortunate to have had multiple definitive mortality trials that have shaped our evidence-based practice. The use of β-blockers in patients with symptomatic heart failure and reduced ejection fraction is firmly based on several RCTs that had all-cause mortality as their primary objective. These major RCTs generated convincing data of the survival-prolonging actions of these agents. The strength of survival-improving data offers the strongest impetus to implement a new therapy into clinical practice to improve public health. As important and convincing as RCTs with the primary end point of all-cause mortality can be, it is impractical to consider that our new therapies will continue to be tested against this highest bar (survival). Indeed, RCTs designed to test whether rates of death are altered by a therapy will, by definition, be confined to only the severest patients with end stages of disease or be prohibitively large in both sample size and duration.

**COMPOSITE CLINICAL OUTCOMES: DEATH AND NONFATAL CLINICAL EVENTS**

Most modern clinical outcomes RCTs are designed to determine whether the intervention alters rates of death and a prespecified combination of important nonfatal events. Incorporating nonfatal events reduces the required sample size and extends the populations that can be examined. The concept is that preventing clinically well-defined and important nonfatal events such as stroke, myocardial infarction, or hospitalization for heart failure would be an important objective. Although not as definitive as death, those who survive one of these clinically impactful, though initially nonfatal events, would, with longer follow-up, have a higher risk of death than those with a more benign course. In general, this assumption is usually correct in that subsequent mortality is severalfold higher in the patients who have had a nonfatal cardiovascular event compared with survivors with a more benign clinical course. Time to the first occurrence of any of the prespecified composites is probably the most commonly used analysis of modern major outcome RCTs. An intrinsic problem with the time-to-first-event analysis of RCTs that utilizes a clinical composite outcome is that the analysis gives equal statistical weight to all of the components of the composite. As such, a more serious event such as death that occurs after any of the nonfatal components is ignored in the primary outcome analysis.

In cardiovascular RCTs, the benefit of using a composite of fatal and nonfatal clinical outcomes often termed MACE (major adverse cardiac events) to increase event rates and reduce sample size can be offset when the influence of the therapeutic modality being tested is not consistent across the prespecified components of the primary outcome. Cogent arguments have been made to narrow the focus of the primary composite to the pattern of events that the therapeutic agent being examined is mechanistically most likely to alter: the so-called cause-specific or targeted events. However, inconsistencies of the effect size and even direction are not uncommon results with composite outcomes. Moreover, when nonfatal end points are dichotomized (yes/no), the broad range of severity of the nonfatal event is not considered. In most RCTs, a myocardial infarction that is detected by a minor troponin elevation has the same weight as one that results in cardiogenic shock. Similarly, stroke from which the patient makes an excellent functional recovery would be statistically considered the same as a disabling stroke.

These issues plague most modern trials and clinicians need to be able to evaluate the totality of evidence generated in the RCT by probing beneath the surface of the primary end point. Clinical judgment must
be used in conjunction with statistical testing to more fully understand the impact of a therapy. With or without formal assignments of weight, clinicians make their own assessments of the contributions of the components of the composite clinical outcome to the primary objective. Indeed, clinical trial experts continue to develop new metrics to consider some of these deficiencies imposed by time to first event of a composite outcome analysis. Major efforts are now under way to also incorporate patient-reported outcomes (PRO) along with clinical event reporting to attempt to achieve a better barometer of potential alterations in the disease progression in clinical trials. These novel approaches to clinical assessments are made to provide a more global assessment of the potential therapeutic impact of the tested intervention.

**USE OF SURROGATES**

As discussed by Anand and Florea in an effort to conduct RCTs that provide an indirect measure of morbidity and mortality without requiring extreme sample sizes and duration of follow-up, surrogates or substitutes for clinical outcome end points have been evaluated. In general, these are readily quantifiable laboratory measures, which, based on epidemiologic data, are correlated with either a favorable or unfavorable clinical outcome. The underlying assumption is that therapeutically produced alterations in the surrogate measure of disease severity would predict in a quantifiable fashion the clinical progression of the disease. There are many attractive advantages to using biologically plausible and, indeed, even epidemiologically important markers of disease severity as end points in clinical trials. In some respects, this approach mirrors individual practice of medicine whereby physicians follow a patient, not by events, but by indirect markers we associate with disease severity or progression. Much needed—indeed essential for drug development—smaller RCTs using surrogate end points provide the basis for dose ranging, hypothesis-generating RCTs necessary for providing a rationale and the preliminary information needed to plan a much larger major clinical outcomes trial. This use of surrogate end points is appropriate and essential for early studies evaluating new therapeutic approaches. However, it must be clearly acknowledged that these surrogate marker planning studies cannot provide sufficient data regarding either the effectiveness of the intervention in improving clinical outcomes or its potential for adverse events, which are both needed for informed therapeutic decisions.

**CLEAR DISSOCIATION BETWEEN THE INFLUENCE ON THE SURROGATE AND THE CLINICAL OUTCOMES**

Unfortunately, there have been numerous discordant findings between therapies that clearly altered an established surrogate marker of disease progression in a favorable direction only to be later found in a

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**Table I. Two warnings concerning the use of surrogate markers in clinical trials.**

More definitive clinical outcome RCT to have either a neutral or even harmful action (Table I). This manuscript will highlight some of these discordant instances in the field of cardiovascular, diabetes, and renal diseases, emphasizing the importance of conducting RCTs with clinical outcomes as the primary objective to obtain the best estimates of both clinical effectiveness as well as safety (Table II, page 135).

**Ventricular premature beats**

The Cardiac Arrhythmia Suppression Trial (CAST) provided one of the early and most profound examples of a therapy that favorably altered a highly respected surrogate and yet had a greatly unanticipated detrimental effect on survival. The epidemiology linking frequency of ventricular premature depolarizations to heightened risk of death in high-risk patients was firmly established. In the 1970s and 1980s, a major effort in caring for patients with acute and chronic myocardial infarction and heart failure was to detect and suppress ventricular arrhythmias. CAST was designed to compare several antiarrhythmic agents for effectiveness in improving survival. Patients with recent myocardial infarction, left ventricular dysfunction, and evidence of frequent ventricular arrhythmias were screened to confirm that their extra-systoles could be suppressed by an antiarrhythmic drug prior to randomization. The primary objective of the RCT was survival, not arrhythmia control. CAST was stopped by its safety committee when it had become clear that those randomized to either antiarrhythmic (encainide or flecainide) were more likely to die than those on placebo. A negative impact on survival was also demonstrated with moricizine, the third antiarrhythmic examined. These counterintuitive and unex-
unexpected findings resulted in a major shift in patient management. It is important to emphasize how entrenched the concept of ventricular arrhythmia suppression was prior to the CAST results and to consider the magnitude of patients that were unwittingly treated with harmful agents.

Ventricular contractility

At approximately the same time, another entrenched icon of cardiovascular perceptions that improving contractility in those with systolic dysfunction heart failure would improve clinical outcomes was similarly abolished by mortality data from RCTs that were sufficiently sized to address clinical outcomes rather than surrogates. With impaired contractility or depressed ejection fraction as the pathophysiologic root for the signs, symptoms, and impaired prognosis of these patients, it was understandable, logical, and highly anticipated that positive inotropic agents that had been shown in small RCTs to improve multiple important surrogates of impaired cardiac performance such as wedge pressure, cardiac output, and left ventricular ejection fraction would result in improved patient outcomes.19-21 The finding of dose-dependent increases in mortality with these agents despite the favorable hemodynamic changes “cast” further distrust on the use of surrogate marker RCTs to direct clinical care.

Blood pressure

Since the historic VA Cooperative trial, blood pressure lowering by pharmacologic therapies has consistently and quantitatively been associated with improved prognosis. However, the limits of this association are being uncovered. In the recently reported Action to Control Cardiovascular Risk in Diabetes–Blood Pressure (ACCORD) Blood Pressure trial, patients with type 2 diabetes mellitus and an average baseline systolic blood pressure of 139 mm Hg, were randomized to intensive vs standard blood pressure control strategies.22 Despite achieving a large blood pressure difference (between-group difference 14 mm Hg), patients randomized to the intensive strategy had no significant reduction in the risk of experiencing the composite outcome of cardiovascular death, nonfatal stroke, or nonfatal myocardial infarction (Figure 1).22 Moreover, this group was more likely to have hypotension, hyperkalemia, or serum creatinine elevations. These findings illustrate the hazards of extrapolating results from a higher to a lower blood pressure range.

Kidney function

The African American Study of Kidney disease and hypertension (AASK) Study Group trial offers another example of a discrepant effect of an intervention on a surrogate and a meaningful clinical end point. The primary end point of the trial was the change in glomerular filtration rate, another established surrogate marker for progression of renal disease and increased risk of death; the prespecified secondary outcomes included mortality and progression to end-stage renal disease. While the patients randomized to amlodipine displayed, at least initially, an increase in glomerular filtration rate (GFR) and better blood pressure control, they demonstrated a higher propensity to progress to a worse outcome of death or end-stage renal disease when compared with ramipril.23 In fact, because of this deleterious effect, the amlodipine arm was stopped early by the Data Safety Monitoring Board.24 Another widely held belief is that reductions in urinary protein excretion, or microalbuminuria, could be
translated into reduction in risk of subsequent clinical events. There is evidence that an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin-II receptor blocker (ARB) reduces the surrogate marker of urinary protein excretion and improves clinical outcomes (increase in serum creatinine, need for dialysis or death).\textsuperscript{25,26} Therapeutic regimens combining both inhibitors of the renin-angiotensin system have been shown in several small studies to reduce the degree of proteinuria, possibly to a greater extent than either agent alone.\textsuperscript{27} However, clinical outcomes RCTs have not shown superiority of this combination. The VALSartan In Acute myocardial INfarcTion (VALIANT) investigators showed that post–myocardial infarction patients with signs and symptoms of heart failure and/or left ventricular systolic dysfunction randomized to a combination of captopril and valsartan experienced more adverse events without any further improvement in survival compared with patients randomized to either of the two agents.\textsuperscript{28}

More recently, in a different patient population, high-risk vascular patients, the ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) tested whether the combination of the angiotensin-converting-enzyme inhibitor ramipril and the ARB telmisartan would be superior to either one alone in reducing the risk of the primary composite outcome (death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure) and demonstrated an increase in adverse events without any associated benefit in the combination arm.\textsuperscript{29} More specifically, to address the mechanistic interaction between the surrogate end point of urinary albumin excretion and a prespecified renal composite outcome (need for dialysis, doubling of serum creatinine or death), the authors showed that despite an expected finding of less increase in urinary albumin excretion with the combination therapy than with ramipril, the primary renal outcome was statistically significantly increased with the combination therapy than with either ramipril or telmisartan.\textsuperscript{30} Had a trial been conducted solely with the intent of determining the effect of combination therapy on proteinuria, the effect on the renal outcomes would have been missed. These results, as whenever there are contrasting effects on a surrogate and a clinical end point, can be explained by unintended effects on the clinical end point (increased renal outcomes) independently from, and not through, the intermediary surrogate marker.\textsuperscript{15}

This, again, emphasizes the caution needed whenever surrogate markers are utilized for expanding or proving the clinical utility of an intervention, and that a clear beneficial effect on hard clinical outcomes needs to be demonstrated.\textsuperscript{31}

**POPULATION-SPECIFIC PROVEN THERAPIES SIMILARLY AFFECTING AN IMPORTANT SURROGATE WITH INCONSISTENT CLINICAL OUTCOMES IN DIFFERENT POPULATIONS**

Low-density lipoprotein (LDL) cholesterol lowering with statins may be considered one of the most reliable associations between a laboratory surrogate and clinical outcomes.\textsuperscript{32} Unquestionably, cardiovascular morbidity has been reduced and mortality improved with the use of statins across a broad range of populations. In the high-risk populations with both manifest cardiovascular disease and elevated LDL, the first clinical outcomes trial in the field—the Scandinavian Simvastatin Survival Study (4S)\textsuperscript{33} provided the most definitive data on both a relative and absolute scale about the benefits of this therapy. Within a very short time, complementary clinical outcome data became available from a series of other clinical outcome RCTs with other statins in patients with prevalent cardiovascular disease and lower cholesterol values as well as those without manifest atherosclerosis (primary prevention). Meta-analyses of these placebo controlled clinical outcome RCTs have shown very consistent morbidity mortality benefits.\textsuperscript{34}

Extrapolation of these clinical benefits through LDL lowering of the other populations requires caution. In patients with symptomatic heart failure, both the Effects of n-3 PUFAs and Rosuvastatin on Mortality-Morbidity of Patients With Symptomatic CHF (GISSI HF) study\textsuperscript{35} and the Controlled ROSuvastatin Multinational Trial in Heart Failure (CORONA)\textsuperscript{36} were well-conducted RCTs designed with sufficient statistical power to detect differences in an important cardiovascular outcome composite. In each trial, the statin (rosuvastatin) was quite effective in reducing LDL, with the statin-treated group manifesting large cholesterol and C-reactive protein (CRP) reductions compared with placebo. However, both trials were neutral on their primary clinical outcomes (GISSI HF: time to death, and time to death or admission to hospital for cardiovascular reasons; and CORONA: death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke). This same drug was, however, effective in reducing cardiovascular events in the justification for the Use of statins in primary Prevention: an Intervention Trial Evaluating Rosuvastatin trial (JUPITER), a primary prevention trial.\textsuperscript{37}
This issue of effectiveness of a therapy on a surrogate without ensuring similar clinical outcomes was also apparent in the two major statin clinical outcome trials conducted in patients on dialysis. The German Diabetes and Dialysis Study (GDDS) compared atorvastatin and placebo, while A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events (AURORA) compared rosuvastatin and placebo. In both cases, the statin was effective in lowering LDL without resulting in a statistically different clinical event rate between the placebo and the statin-treated groups. These four well-done trials introduce the concept of competing risk as well as the difficulties of extrapolating clinical outcome benefits from one population to another even though the direction and magnitude of the apparent favorable change in the surrogate was comparable to other RCTs that showed important reductions in clinical events.

**SAFETY IS MOLECULE-SPECIFIC: SURROGATE MARKER STUDIES ARE GENERALLY INSUFFICIENT TO DETECT SAFETY ISSUES**

The strong association between LDL and atherosclerotic risk and the pervasive assumption coupling LDL lowering with better prognosis placed this particular surrogate in the unique company with blood pressure lowering for international regulatory agencies to consider approval of agents that favorably modify LDL without conducting preapproval pivotal clinical outcome RCTs. As such, a member of the statin class could gain approval predominately on the basis of LDL lowering with less patient drug exposure information than would generally be required for compounds claiming clinical rather than surrogate benefits. Cerivastatin gained regulatory approval on the basis of RCTs targeting LDL lowering and apparent safety within the framework of the more limited total patient-time experience relative to the exposure that would have been obtained when effectiveness in clinical outcomes is required. The approximately tenfold increase in the rare, but dreaded, risk of statin-induced rhabdomyolysis was only uncovered in postmarketing surveillance in a nonresearch setting. This example underscores that the sample size generally needed for the demonstration of an apparent favorable effect on a surrogate can be woefully insufficient for an assessment of the safety of a specific molecule. The corollary is that RCTs large enough to test for modifications of clinical outcomes rather than a surrogate laboratory measurement are required to provide a fuller assessment of safety.

**SURROGATE STUDIES LACK OF SAFETY/HDL RISING**

The Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events (ILLUMINATE) trial provides the most vivid recent example of a pharmacologic therapy favorably influencing a strongly accepted surrogate, yet having adverse consequences on clinical outcomes. In epidemiological studies...

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**Table II. Prominent examples of discrepancies between surrogate end markers and clinical end points.**

Abbreviations: BP, blood pressure; CCB, calcium channel blocker; CV, cardiovascular; ESRD, end stage renal disease; GFR, glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Surrogate</th>
<th>Clinical end point</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAST</td>
<td>Premature ventricular depolarizations ↑</td>
<td>Mortality ↑</td>
</tr>
<tr>
<td>VEST</td>
<td>Cardiac performance ↑</td>
<td>Mortality ↑</td>
</tr>
<tr>
<td>AASK</td>
<td>GFR (CCB) ↑</td>
<td>Death or ESRD ↑</td>
</tr>
<tr>
<td>GDDS</td>
<td>LDL ↓</td>
<td>CV mortality/morbidity ↔</td>
</tr>
<tr>
<td>AURORA</td>
<td>LDL ↓</td>
<td>CV mortality/morbidity ↔</td>
</tr>
<tr>
<td>ILLUMINATE</td>
<td>HDL↑, LDL↓</td>
<td>Mortality ↑</td>
</tr>
<tr>
<td>ONTARGET</td>
<td>Urinary albumin excretion ↓</td>
<td>CV mortality/morbidity ↔</td>
</tr>
<tr>
<td>TREAT</td>
<td>Hemoglobin ↑</td>
<td>Death/CV morbidity/ESRD ↔, Stroke ↑</td>
</tr>
<tr>
<td>ACCORD-BP</td>
<td>BP ↓</td>
<td>Death /CV morbidity ↔</td>
</tr>
</tbody>
</table>

↑ Increased; ↓ Decreased; ↔ Neutral.
logic studies, lower HDL cholesterol is strongly associated with higher risk for atherosclerotic events even with adjustment for other conventional risks factors.\textsuperscript{41} Cholesteryl-ester transfer protein (CETP) inhibitors were developed to block the reverse cholesterol transport pathway and raise high-density lipoprotein (HDL) levels while decreasing LDL levels. Indeed, the magnitude of the HDL increase of approximately 80% was unprecedented and, in addition, there was a further 20% lowering of LDL in those treated with torcetrapib compared with placebo.\textsuperscript{42} These apparently favorable alterations in plasma cholesterol were so profound that on average the group treated with torcetrapib had higher HDL than LDL. However, when examined under the rigors of an RCT of 15,000 patients evaluating clinical outcomes rather than the surrogate of plasma cholesterol, the trial was terminated for safety reasons as the mortality of the active treatment group exceeded that with placebo.\textsuperscript{42}

**ACCEPTANCE OF A SURROGATE CAN STIFLE RESEARCH**

Practicing medicine requires integrating the best available, though incomplete, data to make clinical decisions. Often, results of RCTs from a well-specified population are extrapolated to represent the best available information for the individual patient not represented in the trial. Favorable directional changes in a laboratory measure that have an association with better prognosis offers both the patient and physician feedback of a perceived improvement. In the absence of more definitive benefit/risk data, as is often the case, treatment then becomes directed toward improving the surrogate. In some instances, the perception of benefit becomes so pervasive and opinions so solidified that few are willing to put aside their preconceived notions to participate in clinical research. Indeed, clinical guidelines are of necessity developed on the best available current data, which are admittedly nondefinitive. Most guidelines provide a level of evidence for each of the recommendations with the highest being multiple clinical outcome RCTs.\textsuperscript{43} Unfortunately, this level is relatively infrequent and most recommendations are based on less firm data. However, it is important to note that guidelines are not intended to stifle research, but rather to identify areas where data needed for rational clinical decision making are lacking or inadequate. These guidelines could be used to indicate areas of uncertainty where research should be encouraged. When asking an individual whether or not they wish to voluntarily participate in clinical research, the informed consent process delineates the gaps in our knowledge, the precise question being addressed, and the potential risks of the intervention being examined. Patients consenting to participate in RCTs understand the uncertainty and choose to be part of a process that generates information for future clinical decision-making.

Anemia treatment with erythropoiesis-stimulating agents (ESAs) for patients with chronic kidney disease (CKD) who do not require dialysis represents an area where extrapolations of data from other populations (dialysis and more severe anemia) and assumptions based on epidemiology were for many years the best available data. Small RCTs showing that ESAs were effective in raising hemoglobin provided the basis for their use in moderately anemic CKD patients not requiring dialysis. Practice patterns and guidelines made recommendations for ESA use,\textsuperscript{44} which for some signified that the question had a robust answer. Many felt that placebo-controlled trials with ESAs in these patients were unnecessary and for some even unethical. In the absence of RCT with clinical end points, physicians were basing therapeutic decisions predominantly on consensus opinions.

When clinical outcome RCTs were eventually undertaken in this field, the assumption of benefit was so profound that the trials did not test against placebo. Instead, strategies comparing different hemoglobin targets were the objectives of two major RCTs that assessed clinical outcomes. Correction of Hemoglobin and Outcomes In Renal Insufficiency (CHOIR) found that a strategy to use epoetin alfa to a target of 13.5 g/dL resulted in more patients experiencing the composite end point of death, myocardial infarction, heart failure, or stroke relative to those randomized to a target of 11.3 g/dL.\textsuperscript{45} They reported more deaths and heart failure events in those randomized to the higher hemoglobin target. If true, this would indicate a very narrow therapeutic range for epoetin alfa with a presumed benefit of therapy in the low arm (achieved hemoglobin of 11.3 g/dL), while causing deaths and heart failure in the higher arm (achieved hemoglobin of 12.6 g/dL). The Cardiovascular Risk reduction by Early Anemia Treatment with Epoetin beta (CREATE) also presumed benefits and used two active arms to different targets. This smaller trial also showed numerically more first cardiovascular events in those randomized to higher hemoglobin levels.\textsuperscript{46}

Trial to Reduce cardiovascular Events with Aranesp Therapy (TREAT) was being conducted before the results of CHOIR and CREATE. TREAT was designed as a placebo-controlled
blinded study to ascertain whether the composite cardiovascular morbidity and mortality outcome as well as a composite of death and dialysis outcome would be altered by treating diabetics with anemia (hemoglobin ≤ 11 g/dL). At the start of TREAT, many questioned the ethics of having a placebo group even with ESA rescue should hemoglobin falls below 9 g/dL. With the results of CHOIR and CREATE, the concern shifted to the active therapy arm. However, as the largest of the RCTs, TREAT had accumulated more clinical outcomes data than all other trials combined and provided the most reliable risk-benefit assessment. Despite achieving hemoglobin separation, no differences in the primary cardiovascular or renal composite outcomes were observed. The larger placebo-controlled experience did not show a hazard for death or heart failure, but did show a doubling in the rates of stroke compared with placebo. The prespecified test for assessment of fatigue showed rather modest benefits compared with placebo, providing the physician and patients with critical risk-benefit data needed to make informed decisions. For most patients with moderate anemia not undergoing dialysis, the increased risk for stroke uncovered in this placebo-controlled trial will outweigh the potential benefits. In the absence of placebo-controlled trials, the field would have been led by the false sense of security of comparing two doses of the active therapy, which by design can only lead to a recommendation for using the therapy. This is an example of where use of a surrogate to drive clinical practice was so entrenched as to stifl appropriate placebo-controlled clinical outcomes testing RCTs. The TREAT experience also makes the point that definitive trials should be encouraged rather than second-guessed. Once trials are under way, their Data Safety Monitoring Committee is entrusted with decisions affecting patients in the trial as well as future patients by striving for the robust answer to the tested hypothesis.

**CONCLUSION**

The practice of medicine remains a combination of both art and science. Clinical decisions regarding an individual patient always require extrapolations of best available data. It is unreasonable to expect that major RCTs with clinical outcomes and safety data will be available for all clinical decisions. Favorable modifications in a surrogate marker of disease progression need to be viewed in the context of uncertainty for association with clinical outcomes and for certainty in the inadequacy of safety information. When the surrogate is the best available information to guide clinical decisions, its limitations should be understood and further research encouraged.

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EARLY ATTEMPTS TO UNDERSTAND HOW ATRIAL DISTENSION INDUCES CHANGES IN HEART RATE AND RENAL DIURESES

Understanding the physiological control of cardiovascular homeostasis has engaged the curiosity of scientists for centuries. The story of the discovery of atrial natriuretic peptide is a case in point (Figure 1). An aspect of particular interest has been the possible mechanisms involved in the modulation of cardiac function in relation to changes in pressure and volume in the cardiac atria.

Bainbridge1 was specifically interested in the reflex control of the changes in heart rate induced by large changes in venous inflow, which he termed “venous plethora,” or similar changes in heart rate induced by relatively small changes in atrial pressure, as opposed to changes in volume. Based on extensive canine experiments he concluded that:

the reflex acceleration of the rate of the heart which takes place when the venous inflow is increased in the normal animal

is caused by impulses arising within the heart and the effect of the stimulus is an adequate rise in venous pressure.

The neural basis for these reflex changes in heart rate was identified by Nonindez in 19372 and described in greater detail by Paintal (19533, 19794). He identified four types of sensory receptors present in both left and right atria classifying them as: (i) Type A; (ii) Type B with medullated fibers; (iii) endings with vagal non-medullated fibers; and (iv) endings with fibers running along sympathetic nerves. These neural receptors are found at the junction between the veins with the atrium. The Type B nerve endings respond preferentially to stretch. Numerous experiments in the 1950s and 60s were based on intravenous infusions and perfusions, attempting to determine the reflex pathways of both the right and left atria. There was a wide range of often conflicting observations made using this experimental design. In order to overcome these confounding factors, Linden’s Group in the Department of Physiology at the University of Leeds developed the novel technique of inflating small (2- to 3-mm long) balloons carefully placed at the junction of the pulmonary vein and left atrium. A more complex balloon catheter was devised by Kappagoda et al5 in order to distend the superior vena-caval right atrial junction. A series of studies performed between 1958 and 1979 using the anesthetized canine preparation clarified the role of the autonomic sensory and efferent nerves in mediating cardiac rate and contractile responses to changes in atrial pressure.6,7

In addition to changes in cardiac function induced by increases in atrial pressure (or, more specifically, induced by increases in atrial stretch), other observations were made, which suggested that a rise in atrial pressure could act as “volume receptors.” Based on the observation that such a rise could also regulate extracellular fluid volume by increasing urine flow (Henry et al, 19568). Several techniques were used to study the mechanisms that might be involved in regulating extracellular fluid volume, including negative pressure breathing, immersion in water, as well as distension of the atrium and stretching localized areas
of the atrium. Henry et al., working at the Wright-Patterson air force base in the USA, showed that distension of a balloon in the canine atrium caused a 5- to 7-fold increase in urine flow that waned after 30 minutes (Figure 2). Henry and Pearse attributed the diuretic effects to activation of left atrial stretch receptors via vagal nerves. However, when bilaterally vagotomized nonhuman primates are exposed to water immersion, there is still a marked rise in both urine volume and sodium excretion. Furthermore, this immersion response is not mediated by changes in the circulating level of mineralocorticoids or antidiuretic hormone (ADH).

The mechanism(s) possibly involved in the renal diuretic response to increased atrial pressure were attributed either to neural or humoral factors. The typical experiment, in lightly anesthetized dogs, pioneered by Linden’s Group in Leeds, involved raising left atrial pressure by about 1.3 kPA, which caused a significant rise in urine flow and sodium excretion 10 minutes after atrial distension. Relief of the raised atrial pressure was followed 10 minutes later by a reduction in the increased urine flow, which returned to baseline levels after 30 to 40 minutes. Initially, the Linden Group was convinced that the renal response was due to neurally mediated mechanisms triggered by atrial receptor activation of myelinated vagal fibers. However, denervation of one kidney or autonomic blockade with hexamethonium did not block the diuretic response to raised atrial pressure, so the possibility of a humorally mediated response was also considered. A favorite candidate was ADH. The definitive experiment to test this hypothesis was to study the renal response to raised interatrial pressure after destruction of the pituitary gland. In this preparation, left atrial distension still caused a renal diuresis. Kappagoda, in Linden’s Group, in attempting to identify a humoral mediator, examined the effects of serum extracts taken during renal diuresis in anesthetized dogs using as a bioassay the Malpighian tubule of Rhodnius prolixus (Figure 3). In his 1979 paper summarizing the results of his work, Kappagoda stated “the efferent path of this reflex is indubitably humorally in nature and its identity remains controversial.”

**HISTOLOGICAL STUDIES ON ATRIA**

While the physiological studies briefly summarized above were being performed between 1950 and 1980, other scientific groups were examining the fine structure of atria, the myocardium, and the conduction system. These histological studies were pursued com-
completely independently of the physiological studies. The atrial endocardium has a subendocardial plexus composed of varying sizes of nerve trunks comprising possibly end-nets and unencapsulated nerve endings, which vary according to species and staining technique. The plexus comprises fibers originating from both sympathetic and vagal nerves. Ultrastructural studies in pig atria reveal a range of organelles associated with these nerve fibers including glycogen granules, Golgi-like end-organs, and mitochondria-filled vesicles. Somewhat surprisingly, the authors of related histological studies quoted in these papers to which reference is made failed to mention the existence of large numbers of membrane-bound specific granules which were initially thought to contain lipofuscin and lysosomal granules or catecholamines. Their characterization, based solely on histological studies, is entirely dependent on the staining techniques utilized, which may explain why they were overlooked.

In 1964, Jamieson and Palade published a careful analysis of “specific granules in atrial muscle cells” in which firstly they emphasized that up until that period the atrial mammalian myocardium had been much less extensively studied than the ventricular myocardium. They described large populations of spherical electron-opaque granules (0.3-0.4 μ) found in muscle fibers of mammalian atria (Figure 4).

These granules are absent from the ventricle. They noticed that the granules were intimately connected with the Golgi complex, and carefully analyzed the tissue so as to determine whether the granules contained catecholamine or other material. Several previous publications had claimed that the granules contained catecholamines, but Jamieson and Palade summarized the evidence against this as: (i) ventricular muscle contains catecholamines, but its cells have no granules; (ii) chromaffin reaction fails to demonstrate catecholamines in atrial granules; (iii) autoradiographic studies show no uptake of H3-dopamine; and (iv) do not contain 5-hydroxytryptamine. They emphasized that isolation of the content of the granules would be difficult because they are demonstrated in the rat adrenal medulla. They also published a lengthy review in the same year describing in detail all the studies that had been done previously to identify specific granules in both mammalian and non-mammalian vertebrate cardiocytes. They concluded their critical review by emphasizing that despite intensive study the “secretory nature” of specific granules had not yet been demonstrated. They concluded somewhat prophetically that:

should the actual secretory function of these granules become established, not only would the present concepts of myocardial function need revision, but the regulation of function in more distant organs may be involved.

Thus, by 1979, the physiologists were speculating that pressure changes in the atria lead to changes in renal function, either by neural or humoral mechanisms. Attempts to identify a circulating mediator modulating renal function were unsuccessful. The candidate humoral factors triggered by raised atrial pressure included (i) decreased secretion of AVP, (ii) inhibition of the RAS, (iii) increased secretion of catecholamines and or dopamine, (iv) an ouabain-like factor secreted by the pituitary, and (v) ADH. On the other hand, histological studies performed in Departments of Pathology measuring the granularity of the atria showed that their content changed following differing experimental interventions in rats, such as bilateral adrenalectomy or infusion of sodium chloride. De Bold and Bencosme, having developed a markedly improved morphometric histochemical technique, permitted for the first time the accurate quantification of changes in atrial granularity. In 1979, using this new morphometric technique, de Bold (Figure 5, page 144) published a sole author paper showing that sodium and water deprivation significantly increased atrial granulari-
The discovery of the atrial natriuretic peptides

by 1979/80 several separate scientific investigators were pursuing the identity of a circulating factor, which mediated changes in urinary sodium and volume, triggered by changes in atrial tension or volume. Given the key role of sodium balance in blood pressure control, the identification of a new mediator of blood volume control in addition to the established importance of angiotensin and aldosterone assumed considerable importance. 29

In contrast to the complex experimental physiological studies on cardioenal diuretic mechanisms, several groups used increasingly sophisticated histochemical methods to determine the nature of the atrial granules and quantified changes in different rat models. It was shown by Cantin’s group at the Clinical Research Institute, Montreal, that the atrial granules contained proteins. 30 At the nearby Queen’s University Department of Pathology, Ben-cosme, who had been studying these atrial granules for the past 10 years, recruited Dr de Bold from Argentina to work on the histology of atrial granules for his PhD thesis in 1968. Similarly, Hatt’s group working in Paris showed in 1976 that changes in the oral intake of sodium and water in rats were associated with an increase in atrial granularity after 5 weeks of restricted sodium intake, while treatment with DOCA and increased sodium in the diet caused a significant reduction in atrial granules. 31

Assessing quantitative changes reproducibly in atrial granule content by histological measurements was diffi-cult. Results depended on the age of the rats, the specificity of the histochemical stains, as well as the technique for embedding and sectioning the tissue. These variables were overcome by de Bold, who utilised a combination of embedding, microtome, and highly specific lead-hematoxylin-tartrazine staining methods. In addition, sophisticated statistical software was used in order to ensure precision of the measurements by a light micro-scopic technique. Having improved the precision of measurement, de Bold then performed a complex series of experiments applying the improved morphological methodology to determine the effects on atrial granularity of water deprivation, DOCA injection (1-2.4 mg/kg), and bilateral adrenalectomy. Serial measurements of atrial granularity combined with simultaneous measurement of blood hematocrit measurements showed a significant correlation between changes in hematocrit and the degree of atrial granularity in water-deprived rat experiments, i.e., hypergranularity is accompanied by high hematocrit values. 28

It would seem that by 1979 the scene was set for the characterization of the nature of atrial granules and the relationship between granule changes and cardioenal function. As with so many pivotal scientific discoveries, the answer depended on a seemingly obvious experiment. In this case, de Bold, in collaboration with Sonnenberg’s group in Toronto, studied the effects of atrial and ventricular homogenates on renal function in anesthetized rats. 32,33 The extract was prepared by homogenizing rat atria in phosphate buffer saline and storing the supernatant at –70ºC. Aliquots (2 mL) of either atrial or ventricular supernatant were administered intravenously to anesthetized rats. The atrial extract induced a 30-fold increase in urinary sodium and chloride excretion, accompanied by a 10-fold rise in urine volume (Table 1). 33

Extracts of the rat ventricle did not affect urine function. The simplicity and clarity of the result is reminiscent of Bayliss and Starling’s single experiment in which they scraped mucosal membrane from the duodenum, ground it up with sand and 0.4% HCl, and injected the filtrate, which resulted in an increase in pancreatic secretion. 34 The atrial extract experiment was first published as an abstract in 1980 followed by a more detailed paper in 1981. 33
SUBSEQUENT EVENTS

Predictably, the race was now on to identify the nature of the active principle in the atrial supernatant. A review of the literature on ANP following these two publications on the renal effects of atrial extracts reveals a veritable explosion of scientific interest. This is exemplified in Figure 6, which depicts the number of papers published on ANP between 1980 and 1990. These data may not be strictly accurate since different investigators used different terminologies in order to describe the structure and function of the peptides isolated from the atria. De Bold, who identified a sequence of ANP in 1983, called it cardionatrin I, while Cantin’s group in the Montreal Institute describe their peptides as ANF-H1(73 aa) and cardiodilatin (LEU94-ARG109:106aa). Laragh’s group in New York called atrial natriuretic factor auriculin, while the Japanese group of Inagami at Vanderbilt University, having isolated peptides from the human material, called it atrial natriuretic factor. This apparent confusion in terminology has been described primarily to illustrate the nature of the intense, and probably competitive, scientific interest triggered by de Bold’s initial experiments.

In concert with the literature expansion, there was also an increase in patent activity relating to structure function aspects of ANP. A brief survey of the worldwide database for patents, entitled “atrial peptide,” identified at least 30 patents up to 1990. de Bold’s group was the first to apply for a patent for the circulating form of ANP, in 1983. Patents were granted to Philip Needleman in 1985, while a patent submitted by the University of Kingston on de Bold’s behalf was dated 1987. In the period up to 1990, eight commercial companies issued patents on analogs of atrial peptides, including Merck. Presumably, the basis for this commercial interest was the emerging views on the possible role of ANP in vascular homeostasis, especially essential hypertension. The basis for this view was that ANP had been shown, by 1986, to inhibit the renin-angiotensin system, reduce plasma aldosterone levels, as well as having arterial and venodilator actions.

An early study of ANP in human volunteers from Espiner’s group in Auckland, New Zealand, showed that a bolus injection (100 µg) of synthetic ANP increased urinary sodium and...

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**Table 1. Urinary response to intravenous injection of atrial myocardial extract in rats (compared with ventricular myocardial extracts and vehicle).**

<table>
<thead>
<tr>
<th></th>
<th>VµL/min g kidney wt</th>
<th>ClµEq/min g kidney wt</th>
<th>KµEq/min g kidney wt</th>
<th>NaµEq/min g kidney wt</th>
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<tr>
<td><strong>Before</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(40-60 min)</td>
<td></td>
<td></td>
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<tr>
<td>A</td>
<td>6.52±1.45</td>
<td>334±97</td>
<td>908±213</td>
<td>912±139</td>
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<tr>
<td>B</td>
<td>5.02±1.07</td>
<td>379±105</td>
<td>1011±190</td>
<td>902±138</td>
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<tr>
<td>C</td>
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<td>182±57</td>
<td>444±93</td>
<td>531±103</td>
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<tr>
<td><strong>During</strong></td>
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<tr>
<td>(60-80 min)</td>
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<td></td>
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</tr>
<tr>
<td>A</td>
<td>47.04±5.64**††</td>
<td>7235±689**††</td>
<td>8769±798**††</td>
<td>2145±177**††</td>
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<td>573±199</td>
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<tr>
<td><strong>End</strong></td>
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<tr>
<td>(160-180 min)</td>
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<tr>
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<td>7.25±1.51</td>
<td>1135±190</td>
<td>1581±289</td>
<td>713±74</td>
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<tr>
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</tbody>
</table>

*Statistically significant differences from group B (P<0.01, P<0.001)
†† Statistically significant differences from group C (P<0.01, P<0.001)

V, urine volume; UClV, total chloride excretion; UKV, total potassium excretion; UNaV, total sodium excretion

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![Figure 6. Number of articles on atrial natriuretic peptides per year between 1980 and 1990.](image-url)
The discovery of the atrial natriuretic peptides

Fitzgerald and Fitzgerald

volum e within 30 minutes of administration. Curiously, the peptide was obtained from BACHEM, a US chemical company (αANP28aa). 41 As such, the compound would not have been subject to routine toxicological evaluation. Subsequently, the same investigators reported on the effects in congestive heart failure of a synthetic analog (1LEU-ANP:L364,343) supplied by Merck. The compound reduced arterial pressure and increased cardiac output, but there was no significant increase in urine volume or sodium. 42 Subsequently, synthetic compounds were developed that either inhibited the breakdown of ANP by endogenous endopeptidases, or selectively blocked ANP receptors. 43 These approaches to modulating endogenous ANP did not lead to therapeutic products. The subsequent sophistication of the natriuretic system is summarized in Table II. It shows the impressive and rapid expansion of scientific knowledge arising from de Bold’s atrial extract experiment over the past 30 years. It is yet a further example of the pivotal role of translational medicine in seeking improved therapy. In this instance, the main health-related contribution appears to be in providing validated biomarkers using plasma BNP levels for the assessment of cardiovascular risk, 44 including outcomes in pulmonary embolism, 45 coronary artery events 46 and the management of acute heart failure 47.

The main therapeutic use of ANP has been in the application of recombinant BNP in the management of acute decompensated heart failure. The recombinant BNP compound (nesiritide) has dual actions (Figure 7). Firstly, it causes an increase in glomerular filtration rate by a direct effect in relaxing afferent renal arterial vessels and constriction of efferent arteriols. At the same time it has potent vasodilator actions, reducing systemic blood pressure by arteriovenous vasodilation, and as a consequence reduces glomerular filtration rates. Thus, the net effect of nesiritide in acute decompensated heart failure is critically dose-dependent. Use of high bolus doses of nesiritide, which can acutely reduce symptoms associated with heart failure, results in an increase in the incidence of renal failure and death 48. When nesiritide is used by careful infusion, it has a net beneficial effect. 49 In order to preserve the desirable renal effects and eliminate the systemic hypotension, a novel ANP agonist (CD-NP) is being evaluated in decompensated heart failure for its natriuretic efficacy and improved safety profile. 50 In Japan, ANP is used extensively (ie, carperitide).

**Table II. Brief summary of some properties of natriuretic peptides.**

<table>
<thead>
<tr>
<th>Peptide ligand*</th>
<th>ANP</th>
<th>BNP</th>
<th>CNP</th>
<th>Other family members</th>
</tr>
</thead>
<tbody>
<tr>
<td>Origin</td>
<td>pre pro ANP 1-151</td>
<td>pre pro BNP 1-34</td>
<td>pre pro CNP 1-126</td>
<td>Guanylin Uroguanylin</td>
</tr>
<tr>
<td>Receptor name</td>
<td>NPRA</td>
<td>NPRA</td>
<td>NPRB</td>
<td></td>
</tr>
<tr>
<td>Plasma T½</td>
<td>3 min</td>
<td>21 min</td>
<td>3 min</td>
<td></td>
</tr>
<tr>
<td>Circulating fragments from N-terminal sequence</td>
<td>NT-proANP 1-30</td>
<td>NT-proBNP 1-98</td>
<td>NT-proCNP 1-76</td>
<td></td>
</tr>
<tr>
<td></td>
<td>31-67</td>
<td>1-76</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* numbers refer to the number of amino-acids in each sequence

**Figure 7. The nesiritide molecule.**

**Reflections**

This account of the discovery of ANP illustrates how scientific observation, ie, atrial distension-induced renal diuresis, can focus a single-minded approach to elucidating the physiological mechanisms. The physiological approach is epitomized by Linden’s team, who spent more than 10 years examining the possible neural reflexes involved in the cardioenal response. This is epitomized in the Proceedings of the Leeds symposium held in 1976, which the author attended, on atrial
reflexes, in which the emphasis of the participants was almost exclusively on neural mechanisms. For some inexplicable reason, the literature describing the presence of noncatecholamine atrial granules was not mentioned at the meeting, nor in the subsequently published monograph (1979) on atrial receptors. The histological approach initiated by Palade and maintained by Bencosme focused again single-mindedly on understanding atrial granule function, making no reference in the histological papers to the role of atrial neural networks.

Another unexplained aspect is the failure of the Queen’s University researchers to collaborate with Cantin and Genest, working in the much larger Institute of Clinical Science based in the University of Montreal. It would seem from the sequence of literature publications that the initial interest of Bencosme in atrial histology started before he joined the Department of Pathology in Queen’s University, Kingston, Ontario. He recruited de Bold in 1968 from the National University of Cordoba, in Argentina, where he had graduated in clinical biochemistry, subsequently gaining a PhD in pathology at Queen’s University. Currently he is Director of the Cardiovascular Endocrinology Laboratory in the University of Ottawa Heart Institute. The key experiment showing the natriuretic effects of rat atrial extracts was performed in collaboration with Sonnenberg, at the Department of Physiology, University of Toronto. Sonnenberg’s expertise was in studying renal tubule and medullary duct mechanisms. Following the joint paper with de Bold in 1981, he published several further studies on the renal effects of ANF. The first international symposium on ANF, held in April, 1985, was co-chaired by Sonnenberg and not de Bold. Interestingly, Cantin also published on the nature of atrial granules in 1974 showing their peptidic nature and the effect of salt loading in rats on atrial granularity. Thus, Linden’s group and de Bold all suggested that the effect of atrial distension on renal function was humorally mediated, but only de Bold did the critical proof-of-concept study. Most investigators assumed that the cardiorenal diuretic response, if humorally mediated, involved known factors such as renin (Cantin) or ADH (Linden). The possibility of a peptide hormone of atrial origin was clearly de Bold’s idea. Somewhat inexplicably, Linden published a subsequent paper in 1995 on atrial receptor function, but makes no reference in either paper to de Bold and ANF.

As this article was going to print, the latest paper on ANP published by de Bold was dated March 2010.

POSTSCRIPT

By coincidence, during a visit of the author to Queen’s University in 1976, he met Dr de Bold. De Bold mentioned his work on atrial granules and gave the author a paper describing their noncatecholamine characteristics. Returning to work in ICI Pharmaceuticals Division that year as Biology Director, the author discussed the paper with Dr Harry Gregory, a notable peptide chemist. However, other research priorities prevented following this lead further.

The author was also privileged to be tutored by Professor Ron Linden in the Department of Physiology in Leeds between 1970 and 1972, endeavoring to improve his own cardiovascular experimental skills. Professor Linden was extremely kind and ran an outstanding cardiovascular physiology group. Sadly Professor Linden died on April 11th, 2010.

Many thanks to Miss Inge Bristow for her expert proofreading and correction of the manuscript.

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Surrogate End Points in Heart Failure Trials: Potentials and Limitations

Summaries of Ten Seminal Papers

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1. Surrogate endpoints in clinical trials: definition and operational criteria

2. Role of surrogate end points in the evaluation of drugs for heart failure

3. Mode of death in chronic heart failure. A request and proposition for more accurate classification

4. Surrogate end points in clinical trials: are we being misled?

5. Are surrogate markers adequate to assess cardiovascular disease drugs?
   R. Temple. JAMA. 1999

6. Surrogate end points in heart failure

7. Reliability of ventricular remodeling as a surrogate for use in conjunction with clinical outcomes in heart failure
   M. A. Konstam. Am J Cardiol. 2005

8. Key issues in end point selection for heart failure trials: composite end points
   J. D. Neaton et al. J Card Fail. 2005

9. Influence of nonfatal hospitalization for heart failure on subsequent mortality in patients with chronic heart failure
   S. D. Solomon et al. Circulation. 2007

10. Heart failure as an endpoint in heart failure and non–heart failure cardiovascular clinical trials: the need for a consensus definition

Selection of seminal papers by Inder S. Anand, MD, FRCP, D. Phil (Oxon.), FACC & Viorel G. Florea, MD, PhD, ScD, FACC
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Highlights of the years by Ian Mudway, MD
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Surrogate endpoints in clinical trials: definition and operational criteria

R. L. Prentice

Statistics reign supreme in clinical trials, and this paper discussing the concept of surrogate endpoints written from the perspective of a statistician has particular seminal value. Prentice starts out with an acknowledgement that there are multiple levels that motivate interest in surrogates, including the possible reduction in sample size or trial duration when a rare and distal end point is replaced by a more frequent and proximate end point. Further, in some cases, the true end point measurement may be invasive, uncomfortable, or expensive, so that the surrogate is often preferable from a patient safety viewpoint. Finally, end points that are close in time to the treatment may be more readily interpreted than more distal end points such as death. Thus, clinicians often find it easier to discuss and track the efficacy of treatments based on surrogate end points, such as low-density lipoprotein reduction. In contrast, discussions based on a true end point such as mortality can be very difficult because mortality can be confounded by secondary treatments or comorbidities.

Prentice then details what should be required for a surrogate to be a valid and unambiguous end point. He maintains that it is important to restrict the use of a surrogate to response variables that can substitute for a true response variable for certain purposes, and proposes a restrictive criterion: “Hence, I define a surrogate end point to be a response variable for which a test of the null hypothesis of no relationship to the treatment groups under comparison is also a valid test of the corresponding null hypothesis based on the true end point.”

Prentice notes that this criterion requires the surrogate variable to capture any relationship between the treatment and the true end point. He goes on to develop an operational criterion that involves complicated and sophisticated statistical techniques that are well beyond the general grasp of a clinical cardiologist, but are important “tests” for the validity of a proposed surrogate. He cites several examples that highlight the intent and the practicality of his operational definition, including a response to the National Cancer Institute request for proposals to identify surrogate end points that would allow cancer screening programs to be evaluated in a more timely fashion than would be possible based on mortality rates. He analyzes the examples of tumor response and disease recurrence, which are popular surrogates in cancer treatment trials. In the cardiovascular arena, he cites the possible surrogates for total cardiovascular mortality, such as ejection fraction in trials of thrombolytic agents, blood pressure reduction in trials of antihypertensive drugs, and blood cholesterol levels in trials of cholesterol-lowering drugs. These surrogates satisfy his operational criterion, as long as the treatments do not differentially affect mortality via pathways that bypass the proposed surrogate and, secondly, that the mortality rates do not depend on other treatments.

Prentice concludes with a pessimistic prediction concerning the potential of the surrogate end point concept because the surrogate must have “precisely the same relationship to the true end point under each of the treatment strategies being compared.” He cites the example of the Multiple Risk Factor Intervention Trial (MRFIT) in which important differences in blood pressure, smoking habits, and blood cholesterol between the treatment and control patients did not lead to the anticipated improvements in coronary mortality.
Role of surrogate end points in the evaluation of drugs for heart failure

R. J. Lipicky, M. Packer

*J Am Coll Cardiol.* 1993;22(4 suppl A):179A-184A

This paper is a collaborative effort between a leader in the Division of Cardio-Renal Drug Products in the Center for Drug Evaluation and Research of the Food and Drug Administration and a leader in the development and conduct of many clinical trials. They start with a summary statement about drug approval: “If a drug does not lessen symptoms or prolong life, there would be little support for its approval by a regulatory agency and little reason for its clinical use by physicians.” They focus on two important questions, including whether surrogate end points can be used to distinguish effective from ineffective drugs and secondly, can the use of a surrogate end point provide reliable information about the effect of a drug on symptoms or survival?

The authors point to the well-known results of the Cardiac Arrhythmia Suppression Trial (CAST) and of the Prospective Randomized Milrinone Survival Evaluation (PROMISE) trial, which “considerably weakened our faith in the reliability and validity of surrogate end points in the evaluation of drugs for heart failure.” They next examine the relative merits of various end points that might be considered clinically relevant in the treatment of heart failure (HF), including an assessment of symptoms and functional capacity with the New York Heart Association (NYHA) classification, quality-of-life instruments, and exercise tolerance tests. The discussion on the assessment of survival supports the view also discussed by Temple (see above) that mortality studies are seen as necessary for the assessment of safety, rather than evidence of efficacy.

The final section of this paper discusses the basis for the approval of new drugs in heart failure and looks at an interesting hypothetical situation. A developmental program for a new drug that has characterized the effects on symptoms and survival could have one of four outcomes. Approval would be likely if the drug relieved symptoms and prolonged life. Conversely, there would be no debate about nonapproval if a drug worsened symptoms and reduced life expectancy. But what would happen in the other two scenarios in which the effects on symptoms and survival were discordant? Would a drug be approved if it improved symptoms, but also reduced survival? Many researchers in the field have specifically asked this question of patients and have been able to quantify this tradeoff. Interestingly, because of the disabling nature of HF symptoms, many patients with advanced HF were indeed very willing to accept a reduced survival if their symptoms could be improved. What about the final scenario in which a drug worsened symptoms but improved survival? This type of agent might be considered valuable in patients with very mild symptoms and a longer life expectancy, much like the discussions regarding the use of lipid-lowering drugs and antihypertensive agents.

The authors conclude “From these comments, it should be apparent that drugs are approved on the basis of an assessment of their benefits viewed in the context of their risks.” In other words, there is no prescribed formula and the “totality” of the data must be considered. While this case-by-case approach seems reasonable and appropriate, it also exposes the opportunity for variability in the interpretation and final recommendation by different reviewers and in different time periods.

A large-scale battle breaks out between US forces and local militias in Mogadishu, Somalia; the United Nations Mission in Haiti is prevented from entering the country by the government, triggering resumption of economic sanctions; and American actor River Phoenix dies of a drug overdose at the age of 23.
Information on the cause and mode of death is very important to understand the effects of different treatments and could have a major bearing on new strategies to reduce mortality in heart failure. Further, as the authors point out, the prevention of sudden death may require a different strategy to the prevention of death due to circulatory failure. This statement was certainly prophetic since, in 2009, we now have the widespread use and acceptance of implantable cardioverter-defibrillators, which have been shown conclusively to reduce death due to life-threatening ventricular arrhythmias.

However, data on the cause and mode of death have been reported sporadically and variably. These investigators performed a valuable meta-analysis of 593 studies that reported more than 50 deaths due to chronic heart failure. They kept only 27 studies that included patients with treated symptomatic heart failure and reported results using categories of the cause of death that could be equated with common definitions (the fact that only 27 of 593 studies could be analyzed emphasizes the sporadic and variable nature of death reporting). The principal finding from this analysis was that the proportion of patients dying of progressive heart failure was 43% in studies that only included patients with New York Heart Association (NYHA) Class III-IV heart failure. In contrast, studies that enrolled fewer sick patients (NYHA Class I-II or higher mean left ventricular ejection fraction) showed that deaths due to sudden death and noncardiovascular deaths were more common.

An interesting concept discussed in this paper is the differentiation between mode of death and cause of death. For example, the mode of death can be classified as sudden death, which is defined in most studies as either occurring instantly, or within 15 minutes (or 1 hour) of the onset of new symptoms. Within the mode of sudden death, the cause of death could be an arrhythmia, myocardial infarction (MI), electromechanical dissociation, myocardial rupture, stroke, pulmonary embolism etc.

The authors also point out that a surprising number of studies did not record where the patient died. For example, it is implicit that, for patients who die in the hospital, some event anticipated their death and that there should be some objective information to sort out worsening heart failure, arrhythmias, etc.

Finally, the authors propose a novel classification scheme for death in heart failure, which they term the ACME System. Their simple chart asks for information in 4 domains, including: A) Activity and Place of death (hospital, out of hospital, witnessed); C) Cause of death; M) Mode of death (sudden, circulatory failure, stroke, other cardiovascular, noncardiovascular); and E) Events associated with death (worsening heart failure, preceding chest pain, MI, arrhythmia, syncope, or other vascular event. While interesting, it does not appear that this classification scheme enjoyed widespread adoption among clinical trials. Nonetheless, the authors should be commended for their attempt to enhance consistency and regularity in the reporting of cause and mode of death.

The Taliban capture Kabul in Afghanistan, driving out President Burhanuddin Rabbani; Alija Izetbegović is elected president of Bosnia-Herzegovina; and American musician Bill Monroe, “The Father of Bluegrass,” dies
Summaries of Ten Seminal Papers - Kubo

Surrogate end points in clinical trials: are we being misled?

T. R. Fleming, D. L. DeMets

Ann Intern Med. 1996;125:605-613

One of the strongest “rebuttals” to the use of surrogate end points comes from two biostatisticians with vast experience in the design and execution of clinical trials. In this review, these authors clearly make the point that pivotal phase 3 trials should only include clinical end points and, “…except for rare circumstances in which the validity of the surrogate end point has already been rigorously established, the primary end point should be the true clinical outcome.”

This paper makes a strong argument to stay with the “traditional” clinical end points, which the authors define as “a clinical event relevant to the patient, that is, the event of which the patient is aware and wants to avoid. Examples are death, loss of vision, symptomatic events … and other events causing a reduction in quality of life.”

The authors concede that trials with these outcomes often have a long duration and are expensive, and so they are sympathetic to the consideration of surrogate end points. However, for a surrogate end point to be an effective substitute for the clinical outcome, the effects of the intervention must reliably predict the overall effect on the clinical outcome. It is this requirement that is usually difficult to fulfill and the authors provide examples to illustrate how surrogate end points have been misleading about the true clinical effects. In the cardiovascular arena, the authors cite three well-known examples where reliance on a surrogate was inappropriate. The Cardiac Arrhythmia Suppression Trial (CAST) showed that antiarrhythmic agents could effectively suppress ventricular arrhythmias but lead to an increase in mortality. In heart failure, the Prospective Randomized Milrinone Survival Evaluation (PROMISE) and PROspective randomized Flosequinone Longevity Evaluation (PROFILE) trials showed that milrinone and flosequinan both increased exercise tolerance, but were also associated with an increase in mortality. Further, a meta-analysis of 50 randomized controlled trials showed an average reduction in cholesterol level of 10% and an average reduction in death from coronary heart disease of 9%, but an unintentional increase in noncardiovascular death of 24%.

This review also includes a discussion on the possible mechanisms by which surrogate end points could be misleading. They include the possibility that the surrogate is not the causal pathway of the disease, that there are many causal pathways of the disease (and the intervention affects only one pathway), that the surrogate is not in the pathway of the intervention’s effect, and that the intervention might also affect the true clinical outcome by unintended mechanisms that are independent of the disease process.

The authors provide an informative table that speculates on the reasons for failures of surrogate end points using these 4 possible mechanisms.

Some of the authors’ concluding statements effectively state their case:

• “Effects on surrogate end points often do not predict the true clinical effects of interventions.”
• “The validity of a surrogate end point has rarely been rigorously established.”
• “Surrogate end points should be used where they perform best—in screening for promising new therapies through evaluation of biologic activity in preliminary phase 2 trials.”

René Lacoste, French tennis player and multiple grand slam winner, dies; the civil trial of O. J. Simpson begins in Santa Monica, California; and former Bulgarian president Andrei Lukjanov is assassinated.
Regulating the approval of new drugs is the primary goal of the Center for Drug Evaluation and Research of the Food and Drug Administration (FDA), so it was interesting to have this institution’s views about surrogate end points. Temple notes the use of surrogate end points has been met with rising enthusiasm as well as rising concern. This mixed reception reflects both the potential of surrogates to bring needed treatments to patients many years before trials that depend on mortality and the potential of surrogates to mislead clinicians into adopting therapies that are not effective or even harmful.

The FDA defines a surrogate end point as a “…laboratory measurement or physical sign that is used in therapeutic trials as a substitute for a clinically meaningful end point that is a direct measure of how a patient feels, functions, or survives, and is expected to predict the effect of the therapy.” It is important to note that the Food, Drug, and Cosmetic Act does not specifically define what end points can provide evidence of effectiveness. Indeed, it states that the FDA should approve a drug unless it finds a “lack of substantial evidence (defined as adequate and well-controlled clinical investigations) that the drug will have the effect it is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling.” In 1992, however, an FDA regulation on “accelerated approval” provided some indirect guidance allowing approval based on “an effect on a surrogate end point that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit.”

Temple’s main argument against the use of surrogates, however, is based on a safety issue. He maintains that a drug could have an unexpected unfavorable outcome that can only be assessed with a study that has a sufficient sample size and followed for a sufficient period of time to detect any significant safety issues. He notes that reliance on a surrogate is usually an alternative to a large outcome trial. He argues that the lack of a robust safety database, which usually comes with a large outcome trial, makes the approval process hazardous, which is sometimes expressed by the phrase “there is no surrogate for safety.”

But there is hope for surrogates after all! If the validity of a surrogate is accepted, there are several ways to gather sufficient data on safety that do not require a large randomized trial. Under certain circumstances, it is appropriate to refer to safety data from other closely related populations and data from other related agents in the same population. For example, angiotensin-converting enzyme (ACE) inhibitors had been studied in 7000 patients with symptomatic heart failure and in 95,000 patients with acute myocardial infarction, and these data made it reasonable to conclude that ACE inhibitors would not cause harm in hypertensive patients.

Temple concludes with specific case examples that illustrate FDA practice. The only surrogates used for approval of cardiovascular drugs are blood pressure and serum cholesterol level. For a drug to be approved for heart failure, “…evidence of a symptomatic benefit needs to be supported by showing that there is at least no adverse effect on survival.” Finally, he notes that “surrogate end points are thus neither consistent successes nor consistent failures.”

Are surrogate markers adequate to assess cardiovascular disease drugs?

R. Temple

JAMA. 1999;282:790-795

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1999

M. Night Shyamalan’s film “The Sixth Sense” is released into theaters; Istanbul and northwest Turkey are hit by a 7.4 magnitude earthquake killing more than 17,000; and Apple releases the Power Macintosh G4
Anand et al provide a beautiful summary of the many issues regarding the use of surrogate end points in heart failure trials. Surrogate end points are attractive because they can lead to smaller sample size and shorter trial durations. Nonetheless, there are several risks, including the possibility of an incomplete, inadequate or misleading evaluation. This review comprehensively guides the reader through all of the important issues and also analyzes the potential of suggested surrogate end points for clinical studies of patients with heart failure.

The authors outline the levels of evidence that must be provided for a surrogate end point to be considered an adequate substitute for a real end point. First, there must be a strong and consistent relationship between the surrogate and outcomes. Second, changes in the surrogate should predict a change in the morbid event. Third, there should be a consistent proportionality between the change in the surrogate and the true end point. Finally, these associations need to be replicated in a variety of different populations using a spectrum of therapeutic interventions. To this set of “Koch postulates” the authors also make a strong statement that there must be a sound pathophysiologic basis that connects the surrogate to the primary outcome.

The next part of this paper is a review of several proposed surrogates that have proven not to be reliable, including hemodynamic measurements, ventricular arrhythmias, and autonomic nervous system markers (eg, heart rate variability). There was great interest in peak exercise oxygen uptake as an “objective” assessment of functional capacity. However, the PROspective randomized Milrinone Survival Evaluation (PROMISE) and Randomized Evaluation of Flosequinan on ExerCise Tolerance (REFLECT) trials, which evaluated efficacy showed that milrinone and flosequinan could increase peak oxygen uptake, but also reduce survival. We now know that several trials completed in 2009 failed on this end point so that peak VO₂ has not been considered a viable surrogate. Other trials focused on neurohormones, including norepinephrine, but the Second Prospective Randomized Study of Ibopamine on Mortality (PRIME II) and Beta-blocker Evaluation of Survival sTudy (BEST) trials showed that changes in norepinephrine could go in opposite directions to mortality. The available data in 2002 were highly promising for B-type natriuretic peptide (BNP) as a surrogate. However, more recent data has shown great variability in BNP levels, which make it an unreliable marker for pivotal trials.

Anand et al then summarize the literature addressing the utility of left ventricular (LV) dimensions and ejection fraction (EF). One of the most important studies at that time was a report by Cintron that found a significant and proportionate relationship between the direction and magnitude of change in EF over time and 1-year mortality. The authors state, “Thus, LV dimensions and their derivative EF seem to fulfill most of the criteria for surrogate end points: baseline LV dimensions and EF are significantly related to prognosis; changes in these measurements reflect changes in mortality, and both the direction and the magnitude of change in these variables cause a proportional change in survival.” The reader is referred to the Lead article in this issue, which updates more recent data. Particularly striking is Table III, which shows a significant relationship between the change in left ventricular end-diastolic volume and mortality across many different trials.

The authors conclude “At present, the one perfect surrogate marker for mortality and quality of life in assessing patients with HF remains elusive.” However, there does appear to be a solid foundation for considering LV dimensions and EF.

Controversial Dutch politician Pim Fortuyn is shot dead 9 days before the general election; a remote-control bomb explodes during a holiday parade in Kaspisky, Russia, killing 43 people; and floods ravage Central Europe.
Konstam’s editorial makes a compelling argument that ventricular remodeling deserves strong consideration as a surrogate end point in clinical trials of heart failure patients. This proposal corroborates one of the important recommendations that are described in detail in the summary article by Anand and Florea (see section titled “Ventricular remodeling”).

Ventricular remodeling is characterized by an enlargement of the ventricular chamber, LV hypertrophy, a change from a normal conical shape to an abnormal spherical shape, and a reduction in ejection fraction. It is the characteristic pathophysiologic mechanism underlying the natural course of heart failure. Since it is a direct manifestation of the disease process, it is much more than a simple surrogate. Most importantly, therapeutic interventions that attenuate or reverse remodeling are uniformly associated with improved clinical outcomes (morbidity and mortality). Thus, “…the greatest beneficial impact on clinical outcomes…appears to be caused by those therapies that affect the underlying pathophysiologic process of ventricular remodeling.”

Furthermore, recent updates to heart failure guidelines have focused attention of the need to intervene early to halt the development or progression of clinical heart failure. In these early treatment scenarios, it is not possible to focus on symptoms (there may not be any!) or survival (because it can be so far removed). Instead, benefits are best achieved (and tracked) through interventions that prevent or regress ventricular remodeling.

Konstam provides a summary of many trials of different therapeutic agents that support the above statements. He discusses results from the Vasodilator Heart Failure Trial (V-HeFT), several trials with angiotensin-converting enzyme inhibitors, the accumulating evidence with angiotensin receptor blockers, β-blockers, and recent experience with aldosterone receptor blockers. He also refers to a meta-analysis of 72 trials that demonstrated that changes in ejection fractions and/or left ventricular volumes correlated with drug effects on clinical outcomes, similar to the analysis summarized by Anand. The key here is the consistency of the effect—all the therapies that have beneficial actions on the clinical end points of symptoms and survival also have a beneficial effect on left ventricular remodeling.

Konstam’s closing suggestions are particularly relevant for those involved in the development of clinical trials. These include: “On the basis of the accumulated evidence, this magnitude of reduction in left ventricular volumes…can therefore serve as a surrogate marker… it is feasible to construct trial designs in which composites are constructed between indexes of ventricular structure and/or function and those of clinical outcomes… A drug’s effect in inhibiting or reversing the remodeling process should, at the least, be taken as supportive of the clinical outcome effects…. In this way, recognition of the validity of markers of remodeling as surrogates for clinical outcome can translate into the improved efficiency of drug development and approval.”

It is recognized that the role of ventricular volumes, or indeed any surrogate, will continue to be challenged, especially by the purists who insist on true clinical outcomes. But the accumulated data on the viability of ventricular volumes is strong and compelling for many experts in the field.

Pope John Paul II makes 2005 the International Year of the Eucharist in Catholicism; Four Royal Canadian Mounted Police officers are gunned down in Mayerthorpe, Alberta, Canada in the deadliest day in Canadian law enforcement in over 120 years; and several hundred Iraqis die in a stampede on Al-Aaimmah bridge in Baghdad.
In 2004, the Heart Failure Society of America sponsored a 2-day workshop that brought together a broad representation of academic cardiologists, statisticians, the Food and Drug Administration (FDA), and industry sponsors to discuss many of the common issues and problems that were challenging the design of pivotal trials that were necessary for regulatory approval in the United States. Devices for heart failure were the “hot topic” of the decade, but it became very apparent that there were key issues for device trials that were not relevant in the traditional drug studies. Sponsors had brought forward many innovative devices and trials, but, because they were conducted individually, there was little consistency or coherency.

The main objective of this workshop, then, was to bring all the main groups together to discuss common issues and see if a consensus could be reached on some of the more important trial design issues.

In this paper, Neaton and his colleagues provide a comprehensive review on the use of composite end points in heart failure trials. They draw on their expertise and vast experience serving on steering committees, Data and Safety Monitoring Boards, Clinical Events committees, and also FDA Advisory Panels. They provide an outstanding review on the use of composite end points, and discuss the key advantages and disadvantages of this approach.

The primary rationale for using a composite primary outcome is sample size. In both time-to-event trials and success/failure trials, the use of a composite can lead to a smaller sample size or trial duration. A second reason to use composites is to avoid the problem of competing risks, which is why the end point of hospitalization is typically combined with mortality. It is conceivable that an intervention could reduce the number of hospitalizations because it increased mortality! Thus, combining the outcomes of death and hospitalization into a composite reduces the chance for bias and makes the results more interpretable.

Finally, a composite can help to make sure that the primary end point can be assessed in all patients. For example, if one is assessing quality of life as an end point, one way to account for missing data from patients who die prior to the end of the study is to include death as part of the composite.

This paper also summarizes many of the cautions and potential problems of composites. There can be loss of power if the treatment effect is not similar for all of the components and, even worse, when components of the composite go in opposite directions. A second problem with composites relates to the differential weighting of the individual components. For example, should death be given the same weight as a hospitalization or a change in quality of life? If the composite does assign different relative weight, it is important that the weights be validated against some credible outcome (eg, mortality).

The authors also provide 6 excellent examples from trials that used composite end points to highlight the utility and potential problems from “real life” trials.

It is unfortunate that only one paper came out of this 2-day meeting. But, for all those who are involved in trial design and contemplating the use of a composite end point, this reference is a must read!
Hospitalization rates (both all-cause and heart failure [HF]-specific) are one of the most commonly used end points in HF trials, and the Lead article by Anand and Florea in this Journal provides an excellent summary on how this end point is used in trials and some of the important features to consider in data collection and interpretation of the results. A very common trial design feature is to combine hospitalization with death in a composite end point, in order to avoid misinterpretation of an intervention that reduced hospitalization due to the fact that more patients died.

This paper by Solomon et al is a classic description of additional levels of relation between death and hospitalization. Death removes the sickest patients who are likely to be hospitalized. In addition, as shown in this paper, hospitalization increases the risk of death as well as the risk of subsequent hospitalization. Adding to the complexity, if a device increases survival, it increases the period during which a hospitalization could occur. Thus, statisticians employ nonparametric methods to consider mortality as a competing risk as well as adjusting for follow up time.

This study analyzed data from the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) study, which evaluated the effect of candesartan in three independent, concurrently performed trials of 7599 patients representing a broad spectrum of symptomatic heart failure and either reduced or preserved left ventricular ejection fraction. Data from the CHARM trials were examined to assess the influence of a nonfatal hospitalization for HF on subsequent death. Of the 7572 patients included in this analysis, 1455 had at least one hospitalization. Of the 1891 deaths, 586 occurred after hospital discharge for a first HF hospitalization. The estimated crude hazard for all-cause mortality after HF hospitalization was 4.55 times that of patients never hospitalized. The risk of dying was also related to the length of the HF hospitalization, with long hospitalizations (>22 days) carrying more than double the mortality risk of short HF hospitalizations (<7 days).

The authors discuss important clinical implications of their findings. The high risk of death following hospitalization indicates that patients are particularly vulnerable in the early discharge period and might be candidates for heightened surveillance. Indeed, many programs have been implemented by hospitals across the country that employ early intervention with early clinic visits (within 3 days of discharge) and home visits to detect and treat HF problems. In particular, we have found countless cases where medication reconciliation appeared to have aborted a post-discharge complication.

Further, the observation that hospitalization increases the risk of death and subsequent rehospitalization has been used in the design of many different clinical trials. Thus, if one is designing an intervention that should reduce hospitalizations (eg, hemodynamic monitors; home scales), one important inclusion criterion would be to enroll patients who have been hospitalized in the previous 6 months. This inclusion criterion would have the effect of enriching the number of anticipated events (hospitalizations) and therefore increase the power of the study.

Influence of nonfatal hospitalization for heart failure on subsequent mortality in patients with chronic heart failure


Circulation. 2007;116:1482-1487
Heart failure as an endpoint in heart failure and non–heart failure cardiovascular clinical trials: the need for a consensus definition


Eur Heart J. 2008;29:413-421

Cardiovascular clinical trialists, biostatisticians, National Institutes of Health scientists, regulators, and pharmaceutical industry scientists met to discuss issues that related to the design of clinical trials at a Cardiovascular Clinical Trialists Workshop, in December 2005. These meetings can be very important since they bring all the major stakeholders in a single place to debate strengths and weaknesses and new data. This manuscript summarizes the discussion that focused on the definition of heart failure as an end point.

Several clinical trials have established common criteria to define myocardial infarction and stroke, but a consistent definition for heart failure was lacking. Since different trials used different definitions, it has been difficult to interpret data across trials, determine the true incidence of heart failure, and whether or not there are important trends over time. Some of the challenges, of course, are related to the fact that heart failure is not a single event, like myocardial infarction and stroke, but rather is a clinical syndrome related to multiple causes and with many different clinical manifestations. This review also discusses another level of complexity by highlighting the difference between heart failure and non–heart failure clinical trials. In heart failure trials, the diagnosis of heart failure is already established and so one could use hospitalization or administration of intravenous medications as an indicator of a heart failure event. In contrast, in non–heart failure trials, the diagnosis of heart failure is not established and so hospitalization might not be a very sensitive marker. Moreover, in non–heart failure trials, some documentation of heart dysfunction (eg, echocardiography or B-type natriuretic peptide [BNP] level) would be necessary to be sure that the symptom (eg, edema) is due to heart failure and not some other comorbidity.

This review also contains some useful discussion of several important topics including the utility of adjudication committees who are blinded to treatment assignment to reduce bias and maximize consistency in counting heart failure events. Difficulties with counting heart failure hospitalizations include the fact the thresholds for hospital admission and the administration of intravenous medications differ across institutions and regions of the world. Some trials have attempted to reduce this variability by implementing decision rules for what constitutes a hospitalization and treatment algorithms for different medications, but it is always difficult to implement this level of consistency in a multicenter and multinational clinical trial.

Although the authors state that “it is impractical to create a heart failure definition that is clinically relevant and satisfies all types of trials across multiple disciplines,” they do provide a standard uniform set of criteria that can be used as a framework to define heart failure across trials, that include: (i) objective evidence of cardiac dysfunction (eg, imaging or BNP) and that the patient is receiving treatment; (ii) that the event is clinically meaningful; and (iii) that the event captures the course of the disease. These criteria may not be perfect, but it is clearly easier to move the field forward if all are working from a common platform!
Surrogate End Points in Heart Failure Trials: Potentials and Limitations

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