Hypertension and Diabetes and the Fosinopril Versus Amlodipine Cardiovascular Events Trial (FACET)

More ammunition against surrogate end points

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MEDICAL THERAPY OF CHRONIC DISEASES — The report from the Fosinopril versus Amlodipine Cardiovascular Events Trial (FACET) in this issue of *Diabetes Care* (1) provides further evidence of a major dilemma for clinicians and patients. We can be certain that widespread prescription of therapies for chronic diseases without validation of the true effects of these therapies on major clinical outcomes will, with some frequency, result in proliferation of therapies detrimental to the well being of the patients we are serving. The methodology and the technology now exist to limit this problem; but successful implementation of a strategy to measure the impact of specific therapies on medical outcomes in chronic diseases requires a cultural change in the practice of medicine and a major alteration in the clinical research infrastructure.

If we take this randomized clinical trial (FACET) at face value, we have randomized trial evidence that in patients with diabetes and hypertension, those treated with the ACE inhibitor, fosinopril, have a lower rate of major vascular events than patients treated with the calcium-channel blocker, amlodipine. The measures of renal function, LDL cholesterol and triglycerides, and diabetes control were almost identical in the two groups, providing no clue as to why events would be lowered with fosinopril. However, the systolic blood pressure was lowered significantly more in the amlodipine group, a paradoxical finding if the main mechanism of event prevention in patients with hypertension is lowering the blood pressure. Of interest, the HDL cholesterol rose slightly more with fosinopril, and the fibrinogen dropped somewhat more with fosinopril.

The reader is left with three possible explanations for the observed excess vascular events in patients treated with amlodipine. It is possible that both agents are effective, but fosinopril is more effective than amlodipine in preventing vascular events. Alternatively, perhaps amlodipine is actually detrimental in that it causes an excess of vascular events, and patients would be better off on placebo than on amlodipine. Finally, we cannot exclude the possibility that the findings are simply due to the play of chance. This single trial cannot provide a definitive answer to which of these is true. Nevertheless, careful consideration from this latest chapter in the calcium-channel blocker story is merited.

Old paradigm

In the "traditional" approach to chronic disease therapy, a pathophysiological construct is developed for the disease, the construct is tested in animal models, and therapies that modulate the construct are developed. Therapies are then tested in humans using the construct as the basis for evaluation. Through the construct, surrogate measures are developed that can be used to determine whether the construct is being affected by the treatment. Clinical trials have generally been performed in patients without major complicating factors or risk of major mortal or morbid events; this was the case in the FACET trial, which excluded patients with or at risk of vascular disease. The commonly used justification for this practice is that including high-risk patients would cause a major problem with missing data, since the surrogate cannot be measured in dead patients. In the end, however, a different problem is created, since the sample sizes in studies using pathophysiological surrogate end points are generally too small to detect modest, but important, differences in clinical outcomes. If the surrogates are favorably affected and no evidence of a significant safety problem is found, the therapy is endorsed and allowed "on the market" under the presumption that doctors and patients will be able to figure out how to use the therapy in the more severely ill and complex patients frequently seen in practice, but not studied in the trials; or it is presumed that Phase IV adverse event reporting will detect problems.

This approach is flawed for several reasons. Chronic diseases are usually much more complex than accounted for by linear pathophysiological mechanisms with multifactorial causation and complications. Systemic therapies are also usually more complex than we initially envision, and, indeed, some of the most effective therapies have multiple mechanisms of action that are not understood at the time they are initially developed. ACE inhibitors reduce preload and afterload, produce major changes in systemic neurohormonal status, alter myocardial and vessel wall remodeling, and alter fundamental mechanisms of apoptosis. Beta-blockers have direct myocardial effects, lower myocardial oxygen demand, and blunt neurohormonal surges. Even aspirin is now suspected of having a clinically beneficial effect on inflammatory manifestations in addition to its antiplatelet effects. Additionally, we can now be certain that in chronic diseases, individual clinicians are unlikely to be able to decipher the effects of individual therapies on patient outcomes in a manner that leads to useful tailoring of therapy. Adverse event reporting generally does not include typical

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Received for publication 30 January 1998 and accepted in revised form 3 February 1998.
Abbreviations: FACET, Fosinopril versus Amlodipine Cardiovascular Events Trial.

major cardiovascular events, which are expected anyway in patients with risk factors, making it almost impossible to detect modest mortality differences in an adverse direction. Many detrimental effects of chronic disease therapies have gone undetected for thousands of patient-years of exposure.

The study of patients with diabetes and hypertension in FACET provides an excellent case study of the advantages and disadvantages of this pathophysiologically based approach. For both of these conditions, surrogates have been endorsed by the clinical and regulatory community. For diabetes, the control of glucose is assumed to be synonymous with clinical benefit. In patients with hypertension, it has been assumed that therapies that lower the blood pressure are beneficial. These conditions also have in common that they are risk factors for development of atherosclerosis and its complications. Indeed, the most common causes of death for both conditions are myocardial infarction, stroke, and heart failure. The FACET trial took the interesting approach of measuring two of the surrogates, glucose control to measure effect on diabetes and blood pressure reduction to measure effect on hypertension, and adding lipid modification as a common denominator of importance to both chronic diseases. No difference was seen in measures of glucose control or primary lipid measures, but amlodipine reduced systolic blood pressure to a greater degree.

If the investigators had not measured major cardiovascular events, the conclusion of the study would have been that the agents were equivalent for glucose control, renal function, and lipid measures and that amlodipine was a superior blood pressure lowering agent. Indeed, several recent clinical studies have come to this conclusion. We now have a breakdown in the paradigm: the surrogates and the clinical outcomes are not consonant.

This theme is not new. Therapies for heart failure (2), cardiac arrhythmia (3), antithrombotic therapy (4–6), and myocardial infarct size reduction (7) have been down this same road. Based on surrogate end points, well-intentioned researchers have advocated therapies that proved to be detrimental, and in some cases lethal, when used on a broad scale. Often, clinicians have not been able to determine these errors until properly conducted trials were performed.

New paradigm

Patients, practicing physicians, and health care systems are not primarily interested in surrogate measures. They would like to spend money and energy on treatments that affect meaningful clinical outcomes. One interesting definition of meaningful clinical outcomes is an outcome that can be described by a patient in plain English without the need for a medical interpreter. In the case of diabetes and hypertension, these meaningful clinical outcomes are easy to measure: death, stroke, myocardial infarction, heart failure, and need for dialysis. The primary goal of glucose control in diabetes provides an interesting parallel set of issues. Many different methods are available to lower the blood glucose. Some of these methods result in higher insulin levels, while others lower insulin levels. All have systemic metabolic effects, and the impact of these effects on clinical outcomes that matter to patients is unknown.

Until recently, the concept of studying enough patients to measure a treatment effect on major clinical outcomes was not considered to be possible. Led by the International Study of Infarct Survival (ISIS) investigators (8), cardiovascular researchers around the world demonstrated that tens of thousands of patients could be randomized in routine clinical practices, and the data could be aggregated very quickly at an affordable cost. The more recent availability of global communication systems and dramatic increases in computing power have made the collection and aggregation of even more complex data feasible. The major current limitation is the culture of the clinical community, which has been resistant to the development of common nomenclature and clinical data systems that will allow rapid aggregation of data.

SPECIFIC THERAPIES — FACET adds another solid bit of evidence to support the recommendation that ACE inhibitors should be used as first-line agents in patients with diabetes for the treatment of hypertension. With the substantial body of evidence in cardiovascular disease therapy that ACE inhibitors reduce mortality in patients with left ventricular dysfunction, there is considerable confidence that the effect of ACE inhibitors on cardiovascular end points is not harmful. Furthermore, recent evidence has supported a particularly beneficial effect of ACE inhibitors in post-myocardial infarction patients with diabetes (9). Additionally, patients with diabetes and renal dysfunction not only have improved renal function on ACE inhibitors, but a systematic overview has indicated that survival is also improved (10).

The calcium-channel blocker story is more complex. Initial randomized trials in acute ischemic heart disease were of concern with short-acting dihydroperidine calcium-channel antagonists. Post–myocardial infarction studies showed a definite risk of increased mortality in patients with substantial left ventricular dysfunction. A meta-analysis has found that calcium-channel blockers, and especially short-acting nifedipine, increase the risk of myocardial infarction (11). A series of observational studies have found evidence of increased risk of death in patients with hypertension treated with calcium-channel blockers, but these analyses can only be suggestive because of an inability to be sure that confounders have been handled adequately. Furthermore, the debate about the value of calcium-channel blockers has been clouded by the possible influence of financial interests of the health care experts involved (12).

ISSUES RAISED — This trial raises a number of issues that are generic to the determination of which therapies are effective for chronic diseases. One critical issue is how to interpret small clinical trials with interesting findings. The problems with statistical power in small trials have been well described (13). Perhaps less well described is the somewhat higher chance of extreme findings by chance alone in small trials. The concept of a minimum information mass is attractive, allowing practitioners to be aware when therapies are advocated based on definitive information and when the information is inadequate for the recommendation to be firm.

Additionally, focusing on a secondary end point that happened to reach statistical significance is treacherous for several reasons. The primary end points of FACET were lipids and diabetes control. Although cardiovascular events were prospectively defined, it is clear that no significant differences in major clinical outcomes were expected in a trial of this size. The findings have become news because of the unexpected difference of borderline nominal statistical significance ($P = 0.03$ for a composite end point). A simple correction for multiple comparisons rapidly makes this observation not statistically significant. Given the number of small studies being done around the world comparing calcium-channel blockers with other agents, it is possible that extreme findings that occur by chance will be empha-

sized, while many study results that are not dramatic will not be published. These types of issues provide the rationale for the prospective registration of all clinical trials so that the findings of one trial can be put in the context of all available data on the topic.

Over the past decades, as other cardiovascular surrogates such as arrhythmia suppression have lost their luster, blood pressure lowering, LDL lowering, and glucose lowering have retained their place as accepted surrogate end points. FACET points out the flaw in reasoning for all three. In FACET, the drug that lowered the blood pressure the most and had the same effect on lipids and glucose had the worst clinical outcomes. Imagining other drugs that may lower blood pressure, LDL cholesterol, or glucose and that also increase the risk of stroke or death is not difficult.

Fleming and DeMets (14) have recently reviewed the criteria for a surrogate developed by Prentice (15). Correlation between the proposed surrogate and a clinical outcome is not enough. In addition, the surrogate must explain the full effect of treatment on outcome. A surrogate could fail because it does not involve the same pathophysiological processes that lead to the clinical outcome of interest. The proposed intervention may affect the pathway proposed for the surrogate, but another pathway may exist that affects the end point to a greater extent. An example of this problem arose in the use of antiarrhythmic drugs. Premature ventricular beats are associated with higher risk of death, and antiarrhythmic drugs can reduce premature beats, but many of the drugs actually increase mortality (16), presumably because the premature beats are not the mechanism for sudden death. Most troublesome, the intervention may affect the true end point by mechanisms that were unintended in the design of the therapy, or the intervention may affect another mechanism that is more powerful than the mechanism believed to affect the surrogate. An example of this problem is the belief that inotropic agents would improve survival in patients with heart failure by improving myocardial contractility. Indeed, many drugs that improve contractility actually increase mortality, presumably because they have adverse effects on the neurohormonal system.

PRACTICAL POINTS FOR TODAY

— Pragmatists will argue that we cannot wait for huge trials in every area of medicine before we treat our patients. Although many examples of failed surrogates now exist, one can argue that our old system of biological reasoning and surrogate end points has been reasonably successful. A problem with this argument is that the proof of the validity of a surrogate at any point in time is the demonstration that the surrogate and the clinical end point are both affected by the treatment in the same direction. We might as well spare the intermediate step and simply measure the clinical outcome. If the entire medical community was willing to prescribe therapies for chronic disease only with firm evidence that important clinical outcomes were improved, and if practitioners and health care systems were willing to enroll patients in large simple trials as part of daily practice, then the dilemma raised by small trials such as this one would be rapidly replaced with clear definitions of which therapies are truly effective.

For patients with diabetes and hypertension, ACE inhibitors are clearly beneficial and should be used as a primary therapy. Until further information is available from adequately designed and sized clinical trials, calcium-channel blockers should be used only when ACE inhibitors, beta-blockers, and diuretics are unsuccessful in lowering the blood pressure. Fortunately, a number of these studies are underway, and the answers will be available in the next several years. Given the results of FACET, one could reasonably ask the question of which experiment is more responsible: treating a patient with a calcium-channel blocker for hypertension in preference to an ACE inhibitor (with no way of determining whether the practitioner is increasing or decreasing the risk to the patient) or entering that patient into a clinical trial?

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