Themed Issue: Role of Biomarkers in Drug Development

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Blood Pressure as an Example of a Biomarker That Functions as a Surrogate

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ABSTRACT

There are many important uses of biomarkers in drug development. An area of particular interest is the use of biomarkers as surrogate end points. 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 pressures and adverse cardiovascular outcomes. That plausibility has been supported, however, by the numerous placebo-controlled outcome studies evaluating several pharmacologically distinct agents that showed an effect on stroke and coronary heart disease outcomes from lowering blood pressure.

KEYWORDS: biomarker, surrogate endpoint, blood pressure

INTRODUCTION

Before a drug can be approved by the US Food and Drug Administration (FDA), it must demonstrate “substantial evidence” of effectiveness for uses claimed in labeling. The Food, Drug, and Cosmetic Act defines substantial evidence as “evidence consisting of adequate and well-controlled investigations.” The drug must not only be effective but also be safe under the conditions of use described in labeling.

The regulations do not specify whether evidence of effectiveness must come from an evaluation of actual clinical benefit (eg, reduction in anginal symptoms, reduction in stroke, improvement in survival) or from an evaluation of a surrogate end point that substitutes for such clinical benefit, but the end point has to be clinically meaningful.

In regulations written in 21CFR314.500, Subpart H (Code of Federal Regulations) and in the Food and Drug Administration Modernization Act, the agency gained authority to approve drugs for serious or life-threatening disease with no

good available therapy on the basis of an effect of a drug on a surrogate “reasonably likely” to predict clinical benefit, a standard for surrogates that was explicitly lower than that of established surrogates like blood pressure or low-density lipoprotein (LDL) cholesterol.

Sometimes, if certain conditions are met, a change in a biomarker can function as a surrogate end point in the clinical trials that form the basis of approval of a new drug. There are, however, many other important uses of biomarkers in drug development. They can be used to identify subjects who have disease (diagnostic biomarker) or are at greater risk for disease or some consequence of disease (risk stratification biomarker). They can be used to identify a subgroup of subjects likely to respond to a drug. They can also be used in early clinical development to support the mechanistic hypothesis that led to development of the drug or can be used to predict toxicity (eg, predicting the risk of torsades de pointes via QT interval prolongation on a surface electrocardiogram). Such information can help determine whether to pursue development or to terminate development early. In addition, biomarkers may be used to estimate a dose-response relationship preliminarily and to determine doses of a new drug to carry forward into later clinical studies.

An area of particular interest—one that is the focus of this report—is the use of biomarkers as surrogate end points. The obvious reasons are that reliance on surrogates can decrease the cost of development and make drugs available earlier. This report will not attempt to address the larger issue of the general basis for reliance on a surrogate but will use blood pressure, generally accepted as a surrogate end point both by clinicians and regulators, to illustrate a particular case in which a surrogate is acceptable.

BIOMARKERS AND SURROGATES: DEFINITIONS AND EXAMPLES

Before considering the basis for accepting change in blood pressure as a surrogate end point for clinical benefit, it is important to define biomarkers and surrogate end points. Biomarker is a much broader term, including everything from binding affinity, to genotype, to measures that predict clinical outcomes. A National Institutes of Health biomarker working group has defined a biomarker as “a characteristic

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that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.”¹ As the definition suggests, there are many types of biomarkers, including biochemical markers, physiologic markers, anatomic markers, histologic markers, and physical markers. Table 1 lists some examples of cardiovascular and renal biomarkers.

A surrogate end point is a change in a biomarker that can substitute for an observed clinically meaningful end point in the evaluation of the effectiveness of a therapeutic agent. Only a small minority of biomarkers (or changes in biomarkers) are established surrogate end points. One definition of a surrogate end point is “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.”² The effect on the surrogate end point (eg, blood pressure reduction) is not itself of benefit to the patient. That is, people do not usually feel better immediately when their blood pressure or LDL cholesterol is lowered by drugs. Instead, treatment of the surrogate is of value only if the expected effect on a clinical outcome actually occurs. Table 2 lists examples of surrogate end points that relate to cardiovascular and renal drugs and are accepted by the agency. There are, of course, plausible effects on biomarkers (eg, ventricular premature beat suppression post–myocardial infarction or improved cardiac output in heart failure) that have not proven to predict clinical benefit.^{3,4}

Effects on biomarkers become established surrogates in various ways. For example, serum creatinine is a direct measure

of renal function—what might be called a physiologic or functional measure of the integrity of the kidney. It is not hard to conclude that decreasing the rate of increase in serum creatinine in people with diabetic nephropathy would lead to a decreased rate of renal failure, and the early studies of captopril in type 1 diabetics showed this to be true. Other potential surrogates, such as blood pressure or LDL cholesterol, were controversial because they were not direct measures of stroke or coronary artery disease and because there were doubts as to whether improving them would be beneficial. In the 1930s, Paul Dudley White, one of the founders of the American Heart Association, stated that “hypertension may be an important compensatory mechanism which should not be tampered with, even if it were certain that we could control it,”⁵ and such views continued to be heard into the 1960s⁶ and 1970s.⁷

For surrogates that lack a clear physiologic or functional correlate (eg, creatinine), the process of establishing a biomarker as a surrogate end point has generally involved 3 stages. First, there is biologic plausibility, sometimes intuitive, sometimes supported by animal data or by favorable responses in extreme cases (eg, malignant hypertension). Second, there are epidemiologic or natural history data demonstrating that increases (or decreases) in the putative surrogate are correlated with unfavorable (or favorable) clinical outcomes. The correlation between a putative surrogate and clinical outcomes of interest has been identified by Prentice⁸ as 1 of 2 main criteria in establishing a surrogate end point. But while correlation is necessary, it is not sufficient. As stated by Fleming and DeMets, “a correlate does not a surrogate make,”⁹ because the correlation may not reflect causality. In the case of blood pressure, for example, the epidemiologic studies cannot alone reveal whether blood pressure elevation is the cause of cardiovascular disease or is itself benign and is simply a consequence of some other risk factor that is the cause of cardiovascular disease.

Prentice identified a second main criterion for a surrogate: the putative surrogate should fully capture the effect of treatment on clinical outcomes. In other words, it is important to demonstrate from controlled clinical trials that changes in the putative surrogate resulting from at least 1 type of intervention, and preferably many types, working by different mechanisms, affect clinical outcomes in a predictable manner that is fully accounted for by the effect on the surrogate. This is a very demanding criterion. As will be emphasized later, it must always be appreciated that the pharmacologic effect on the surrogate and ultimately on the outcome of interest is often not the only effect of the drug; there may be other effects that can be adverse (eg, hypokalemia with high-dose diuretics) or favorable (eg, effects on heart failure unrelated to blood pressure effects with some antihypertensives).

Table 1. Examples of Biomarkers Used in Cardiovascular and Renal Drug Development

Type of Biomarker	Examples
Biochemical markers	high-sensitivity, C-reactive peptide, plasma B-type natriuretic peptide, plasma homocysteine, urinary albumin excretion, plasma renin activity
Physiologic markers	Blood pressure, heart rate, pulmonary artery pressure, pulmonary capillary wedge pressures, ventricular premature beats
Anatomic measures	Coronary vessel diameter (by coronary angiography), carotid intima media thickness (ultrasound), atherosclerotic plaque burden (intravascular ultrasound)
Histologic markers	Tissue biopsy specimens
Physical markers	Skin color, weight, height

Table 2. Examples of Surrogate End Points Used in Cardiovascular and Renal Drug Development

Surrogate Marker	Predicted Clinical Outcome
Blood pressure	Lowering an elevated blood pressure is predictive of a reduced risk of stroke and coronary heart disease.
Serum creatinine	Delaying a time to doubling of serum creatinine is predictive of a delay in end-stage renal disease, need for dialysis, or other renal replacement therapy.
Serum lipids	Lowering of elevated serum lipids (eg, low-density lipoprotein) is predictive of a reduced risk of stroke and coronary heart disease.
Serum phosphorous	In dialysis patients, lowering of elevated serum phosphorous levels prevents complications of metastatic calcifications and hyperparathyroidism.

EPIDEMIOLOGY OF HYPERTENSION

The relationship between blood pressure and cardiovascular mortality and morbidity (eg, heart failure, angina, myocardial infarction, stroke, aortic dissection, renal failure) has been shown to be consistent in multiple observational studies and to be present for sex, age, and race subsets of the population. A meta-analysis of 9 studies published by MacMahon et al documented the association between diastolic blood pressure (DBP) and stroke and coronary heart disease (CHD) in over 400 000 subjects.¹⁰ The study subjects were predominantly North American males (96%) who did not have a history of stroke or myocardial infarction at baseline. The study found that there was a positive, continuous, log-linear relationship between DBP and stroke/CHD events within the range of DBP 70 to 110 mmHg. The relationship between blood pressure and cardiovascular morbidity/mortality is not sex-specific. An analysis of the Framingham study showed that hypertensive women also are at increased risk for major cardiovascular disease outcomes, including cardiac failure, stroke, CHD, and peripheral arterial disease.¹¹ The relationship between blood pressure and cardiovascular morbidity/mortality is also not limited to any particular race. An analysis of the Multiple Risk Factor Intervention Trial (MRFIT) data that included black males showed a correlation between DBP and death rates from stroke.^{12,13} Additionally, an analysis of the relationship between blood pressure and CHD mortality in 6 different regions of the world showed that although there were differences in CHD mortality that varied by a factor of 3 across the different regions, the risk of CHD mortality increased with increasing systolic blood pressure in every region.¹⁴ The MRFIT data also showed that the relationship between blood pressure and cardiovascular mortality and morbidity is also present at all ages.¹⁵ The relationship between blood pressure and adverse cardiovascular outcomes is not limited to any particular parameter used to assess blood pressure (systolic and diastolic, systolic alone, or diastolic alone). In particular, while for decades diastolic pressure was used to define hypertension, systolic pressure has proven at least equally predictive of outcomes, and it is clear that the high systolic pressure seen in older people is not benign.^{16,17}

CLINICAL TRIAL DATA ON OUTCOMES

The benefits of pharmacologic lowering of blood pressure have been demonstrated in numerous randomized placebo- or active-controlled trials of substantial size that used a variety of pharmacologic agents or classes of agents. Regardless of the pharmacologic mechanism by which blood pressure lowering occurs, the most consistent benefit demonstrated has been reduction of stroke and coronary heart disease. Table 3 provides a list of prospective, randomized, mostly placebo-controlled trials conducted over the last 3 to 4 decades that demonstrate the benefit of antihypertensive therapy. As shown in the table, a variety of pharmacologic agents have been represented, including diuretics, beta-adrenergic receptor blockers, angiotension converting enzyme (ACE) inhibitors, calcium channel blockers, and angiotensin receptor blockers.¹⁶⁻²⁹ The fact that similar results have emerged from studies that used pharmacologically distinct agents provides strong evidence that it is the effect on blood pressure, not some other property of the drugs, that mediates the beneficial effects seen.

LIMITATIONS OF SURROGATES

The general limitations of relying on a surrogate end point or a putative surrogate have been described.⁹ The possibility that the pharmacologic effect on the surrogate will not affect the desired outcome has been alluded to earlier in this report. As noted, the many different pharmacologic interventions that lead to the same outcome strongly indicate that it is the effect on blood pressure itself that leads to the favorable outcome. That does not mean, however, that all interventions will have the same outcome effect for a given change in blood pressure, because drugs can have additional effects, independent of the effect on the surrogate, and these can influence clinical outcomes. This may not be so surprising, as drugs often have unexpected additional effects, either beneficial or harmful.

As an example, the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) study

Table 3. List of Controlled Clinical Trials Evaluating the Effect of Antihypertensive Therapy on Clinical Outcomes*

Study and Publication Year	Population	Active Treatment	Control Treatment	Results
VA Co-op Study 1, 1967	N = 143, DBP 115 to 129 mmHg	HCTZ + reserpine + hydralazine	Placebo	↓ Morbid events (eg, dissecting aortic aneurysm, hypertensive retinopathy, renal function decline, hemorrhagic stroke)
VA Co-op Study 2, 1970	N = 380, DBP 90-114 mmHg	HCTZ + reserpine + hydralazine	Placebo	↓ Morbid events ↓ Strokes ↓ Heart failure
Hypertension Detection and Follow-up Program, 1979	N = 10 940, DBP ≥ 95 mmHg at baseline	Stepped care: more aggressive BP lowering with goal DBP < 90 mmHg for subjects with baseline DBP > 100 mg Chlorthalidone ± triamterene or spironolactone (first line)	Referred care: standard of care or less “aggressive” control	↓ All-cause mortality
Australian Therapeutic Trial in Mild Hypertension, 1980	N = 3427, DBP 95-109 mmHg	Chlorothiazide (first line)	Placebo	↓ CV mortality ↓ Fatal/nonfatal stroke
MRC trial, 1985	N = 17 354, DBP 90-109 mmHg	Bendrofluazide (first line) Propranolol (first line)	Placebo	↓ Stroke
EWPHE, 1985	N = 840, age > 60 years old, SBP and DBP 160-239 and 90-119 mmHg, respectively	HCTZ + triamterene (first line)	Placebo	↓ CV mortality ↓ CHF ↓ Nonfatal stroke
Randomized trial of treatment of hypertension in elderly, 1986	N = 884, SBP > 170 mmHg and DBP > 105 mmHg (at initial screening), ages 60-79	Atenolol (first line)	Standard of care	↓ Fatal/nonfatal stroke
SHEP, 1991	N = 4736, isolated systolic hypertension	Chlorthalidone (first line)	Placebo	↓ Stroke ↓ CHD
STOP-Hypertension Trial, 1991	N = 1627, ages 70-84 years, SBP 180-210 mmHg and DBP at least 90 mmHg or DBP 105-120 mmHg alone	Atenolol (first line) HCTZ + amiloride (first line) Metoprolol (first line) Pindolol (first line)	Placebo	↓ Stroke ↓ CHD
MRC-O trial, 1992	N = 4396, ages 65-74 years, SBP 160-209 mmHg and DBP < 115 mmHg	HCTZ + amiloride (first line) Atenolol (first line)	Placebo	↓ Stroke ↓ CV events

Continued

Table 3. Continued

Study and Publication Year	Population	Active Treatment	Control Treatment	Results
Syst-EUR, 1997	N = 4695, age > 60 years, SBP 160-219 mmHg and DBP < 95 mmHg	Nitrendipine (first line)	Placebo	↓ Stroke ↓ CHD
UKPDS 38, 1998	N = 1148, hypertensive, type 2 diabetes (subset of subjects recruited to UKPDS study)	“Tight” BP control with captopril (first line) or atenolol (first line)	“Less tight” BP control	↓ Stroke
HOPE, 2000	N = 9297, age > 55, with vascular disease or diabetes (~47% with history of hypertension at baseline)	Ramipril (first line)	Placebo	↓ Stroke ↓ CV death
LIFE, 2002	N = 9193, ages 55-80, SBP 160-200 mmHg, DBP 95-115 mmHg and LVH	Losartan (first line)	Atenolol	↓ Stroke

*The symbol ↓ represents a statistically significant difference with a nominal *P* value of < .05. “First line” refers to the initial antihypertensive therapy begun in study subjects. Additional antihypertensive agents could have been added if blood pressure was not adequately controlled. VA indicates Veterans Administration; DBP, diastolic BP; HCTZ, hydrochlorothiazide; BP, blood pressure; CV, cardiovascular; MRC, Medical Research Council; EWPHE, European Working Party on High Blood Pressure in the Elderly; SBP, systolic BP; CHF, congestive heart failure; SHEP, Systolic Hypertension in Elderly Program; CHD, coronary heart disease; STOP, Swedish Trial in Older Patients with Hypertension; MRC-O, Medical Research Council Trial of Hypertension in Older Adults; Syst-EUR, Systolic Hypertension in Europe Trial; UKPDS, United Kingdom Prospective Diabetes Study Group; HOPE, Heart Outcomes Prevention Evaluation Study; LIFE, Losartan Intervention for Endpoint Reduction Trial; LVH, left ventricular hypertrophy.

was a randomized, blinded, active-controlled hypertension outcome study that compared the efficacy of 4 antihypertensive agents (chlorthalidone, lisinopril, amlodipine, and doxazosin) on the primary outcome of CHD mortality and nonfatal myocardial infarction. The agents could not be distinguished for this end point, but doxazosin had a relative risk of congestive heart failure that was 2.04-fold (95% CI → 1.79–2.32) higher than that of chlorthalidone.³⁰ This is not an example of a failed surrogate, but it does highlight the fact that drugs can have additional effects on clinical outcomes of interest.

In another example, the Irbesartan Diabetic Nephropathy Trial (IDNT) study³¹ showed that in hypertensive patients with type 2 diabetes mellitus, irbesartan reduced the risk of progression to doubling of serum creatinine and onset of end-stage renal disease relative to placebo. The blood pressure lowering with amlodipine, the active comparator in the IDNT study, was similar in magnitude to that of irbesartan. Despite the similar antihypertensive effect, however, amlodipine could not be distinguished from placebo in

its effects on progression to doubling of serum creatinine and progression to end-stage renal disease.

There is now great interest in whether some individual agents or antihypertensive regimens yield better outcome results than others.³²⁻³⁴ Recent reports from studies such as Losartan Intervention for Endpoint Reduction Trial (LIFE),²⁹ which have compared the blood pressure-lowering effects of losartan and atenolol in hypertensive patients with left ventricular hypertrophy, have suggested that atenolol has a smaller effect than losartan does on stroke. The issue is still unresolved, however.

Thus, even the use of a well-established surrogate cannot guarantee that there will not be differences in clinical outcomes between treatments with similar effects on the surrogate. Similar issues arise in other cases. For example, there is active discussion of whether the effects of 3 hydroxy-3 methyl glutaryl coenzyme (HMG CoA) reductase inhibitors (statins) on LDL cholesterol fully account for the drugs' effects on clinical outcomes or whether there are additional effects (eg, antiinflammatory effects) that

contribute to clinical benefit and are not captured by LDL effects.

SUBPART H APPROVAL

In 1992, the FDA published a final rule³⁵ that put in place a new mechanism for approval of drugs: Subpart H, the accelerated approval of new drugs for serious or life-threatening illnesses. Accelerated approval allows the agency to base marketing approval on a drug's effect on a "surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit." Subpart H approval is limited to diseases that are "serious or life-threatening" and that lack good available therapy. The "reasonably likely" standard is interesting in that it is clearly stated that this is a lower standard than that used for surrogates for full approval (eg, blood pressure, LDL cholesterol), but the "usual" standard is nowhere defined in regulations. The rule states that there should be evidence of biologic plausibility and some natural history or epidemiologic evidence demonstrating the association of the surrogate and clinical outcomes. Approval under Subpart H is subject to the requirement that the sponsor conduct postmarketing clinical studies to "verify and describe the drug's clinical benefit and to resolve remaining uncertainty as to the relation of the surrogate endpoint upon which approval was based to clinical benefit, or the observed clinical benefit to ultimate clinical outcome."³⁵

CONCLUSION

Biomarkers have well-established, valuable roles in drug development, including helping to identify patients at risk for disease, select doses for study, identify patients likely to respond to therapy, and monitor disease activity. In addition, when certain criteria are met, effects on biomarkers can function as surrogate end points that can be studied in well-controlled trials and used as a basis for approval. In this report, we have discussed blood pressure as an example of a biomarker that has become a well-established surrogate end point, on the basis of natural history/epidemiologic data and numerous placebo-or active-controlled outcome trials of a variety of agents that correlate reductions in blood pressure with reductions in the risk of cardiovascular events. Blood pressure, as a surrogate end point, is unusual in that many drugs for blood pressure (eg, thiazides, methyldopa, reserpine, hydralazine, guanethidine) were approved before there was an effectiveness requirement (1962) and before there was clinical trial evidence of benefit from control of blood pressure (1967).

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