Commentary

Debate: Are surrogate end-point studies worth the effort?

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Abstract

Surrogate end-points of cardiovascular disease can provide useful information in cross-sectional, prospective and interventional studies. They provide information on association with risk factors, natural history and factors associated with disease progression. Because every participant can reach an end-point, sufficient power can be attained with much smaller numbers of subjects in surrogate end-point studies than in studies that use clinical end-points, so that the costs are likely to be substantially less. Measures of carotid intima–media thickness (IMT) by B-mode ultrasonography and of coronary calcification by electron beam computed tomography (EBCT) appear to be the most promising surrogate end-points.

Keywords: cardiovascular events, coronary angiography, electron beam computed tomography, intima–media thickness, surrogate end-points

Introduction

Although cardiovascular disease is the commonest cause of death in Western countries, the large number of cardiovascular events result from a low absolute event rate in a large number of people. Prospective trials that assess the effect of an intervention on event rate therefore require large numbers of subjects to be followed for many years, at huge expense. This has led investigators to use surrogate end-points. With the use of surrogate end-points, every participant can reach an end-point, which is usually a continuous rather than a categorical variable. As a result, sufficient power can be attained by studying much smaller numbers of subjects for shorter periods of time. There are, however, inherent problems with this approach. The validity of a surrogate end-point must be established. This in itself requires a prospective study, adequately powered, to demonstrate that the surrogate end-point is able to predict future cardiovascular events. Furthermore, for a surrogate end-point to be worthwhile, its ability to predict future cardiovascular events must exceed that of conventional risk factors.

Surrogate end-points that have been used to assess the risk of cardiovascular events, and to which this commentary will be restricted, include the following: resting 12-lead electrocardiogram; coronary artery luminal diameters assessed by coronary angiography; arterial stiffness assessed directly, as change in luminal diameter during the cardiac cycle adjusted for lumen diameter and pulse pressure, or indirectly, as pulse wave velocity; brachial artery flow-mediated dilatation; carotid and femoral artery IMT; and coronary artery calcification detected by EBCT.

CHD = coronary heart disease; EBCT = electron beam computed tomography; IMT = intima–media thickness; LDL = low-density lipoprotein.

Resting 12-lead electrocardiogram

One of the early surrogate end-points was the resting 12-lead electrocardiogram. In the Honolulu heart programme [1] both major and minor electrocardiogram abnormalities were predictive of subsequent coronary heart disease (CHD) events. Minnesota-coded ECG events were also used in the 10-year follow up of the Bedford survey of cardiovascular disease in relation to impaired glucose tolerance and diabetes [2]. However, minor electrocardiogram abnormalities such as T-wave changes can be nonspecific, and it can be difficult to demonstrate progression or regression of CHD.

Coronary arteriography

There is a poor relationship between the severity of coronary lesions and their likelihood to cause subsequent cardiac events. Angiograms from patients before they had had a myocardial infarction showed that the median percentage stenosis at infarct-related lesions was only 48%, and that only 22% of the infarct-related lesions had a degree of stenosis greater than 70% [3]. Coronary artery luminal diameters assessed by coronary angiography were used in the Familial Atherosclerosis Treatment Study [4]. Men with coronary disease ($n = 120$) were randomized to two different cholesterol-reducing treatment regimens or placebo. Regression of disease was more common in the treatment groups. Degrees of stenoses were reduced by 0.3 and 1.1% in the treatment groups, whereas there was a 2% increase in the placebo group. Despite the small changes in angiographic appearances, there was a 73% reduction in clinical events in the treatment group compared with the placebo group. Several other intervention studies have used angiography as a surrogate marker for cardiovascular outcomes.

What has emerged is that the small angiographic changes seen do not correlate with the marked reductions in cardiovascular events. Thus, the relationship between degree of stenosis and subsequent myocardial infarction and the relationship of the relatively small changes seen during intervention to the much larger effects on clinical events do not suggest that coronary angiography is an ideal surrogate end-point for cardiovascular intervention studies.

Brachial artery flow-mediated dilatation and arterial stiffness

Data from an autopsy study [5] demonstrated that atherosclerotic involvement of vessels correlates with arterial stiffness assessed noninvasively before death. An association between aortic stiffness and the degree of coronary artery disease assessed at coronary angiography has also been reported [6]. However, no prospective studies assessing the ability of measurements of arterial stiffness to predict future cardiovascular events have been reported.

Brachial artery flow-mediated dilatation, or endothelium-dependent dilatation, may be induced by reactive hyperaemia after vessel occlusion and release. Although flow-mediated dilatation has been shown to be reduced in groups known to be at high risk of CHD, such as individuals with familial hypercholesterolaemia [7] and diabetes [8], its ability to predict future events has not been assessed prospectively.

Arterial intima–media thickness assessed by B-mode ultrasonography

With use of B-mode ultrasonography, the combined thickness of the intima and media, the IMT, can be assessed. The carotid and femoral arteries are most suitable for study because of their superficial localization, size and limited movement.

Increased common carotid IMT is associated with several cardiovascular risk factors, including age, male sex, diabetes, total cholesterol and smoking. It also appears to be an indicator for atherosclerosis in other arteries, including coronary and lower limb [9].

In a prospective study in 1257 men [10] for each 0.1-mm increase in IMT, the risk of acute myocardial infarction increased by 11% ($P < 0.001$). Furthermore, carotid IMT was measured in 5858 individuals who were 65 years of age and older [11]; the relative risk of new myocardial infarction or stroke for the quintile with the highest IMT as compared with the lowest quintile was 3.87.

When carotid IMT was measured on the day of coronary angiography, only a weak correlation was found between coronary artery disease severity assessed angiographically and carotid IMT ($r = 0.26$; $P < 0.0001$) [12]. This may, however, reflect the inadequacy of coronary angiography, rather than that of carotid IMT, to predict cardiovascular events.

Although atherosclerosis predominantly affects the intima, ultrasound imaging cannot discriminate between the intima and the media of the vessel wall [13]. Therefore, in diseases associated with medial thickening, changes in IMT may be less representative of changes in cardiovascular risk. Glycation of extracellular matrix in diabetes may increase medial thickness [14]. We found IMT to be a less useful surrogate marker of CHD than the 12-lead electrocardiogram in an intervention study comparing bezafibrate to placebo in type 2 diabetic persons [15].

If a plaque is located at the site of IMT measurement, the plaque thickness is included in the IMT value. Some studies have used categorical measures of wall status instead of IMT. Belcaro *et al* [16] derived an arterial ultrasound score based on the wall appearance of both carotid and both femoral arteries. In a prospective study, 2000

asymptomatic men with normal serum lipids were followed for 6 years. Arterial ultrasound score was strongly predictive of subsequent cardiovascular events.

Several prospective studies with cholesterol-lowering drugs have shown that reduction in low-density lipoprotein (LDL)-cholesterol was associated with either reduction in progression of IMT or regression of IMT, and associated with reduced cardiovascular events in the treated groups compare with placebo. The Cholesterol Lowering Atherosclerosis Study [17] was a randomized, placebo-controlled angiographic study that tested colestipol-niacin plus diet in nonsmoking men with previous coronary bypass surgery. In this study a subset of 78 individuals also had carotid ultrasound measurements. Drug-treated subjects showed a significant progressive reduction in carotid IMT at 2 and 4 years. In the Pravastatin Lipids and Atherosclerosis in the Carotid Arteries II study [18], individuals with moderately elevated LDL-cholesterol, coronary artery disease and early evidence of carotid arterial disease measured ultrasonically were randomized to receive placebo or pravastatin. Regression of carotid IMT with reduction in both coronary and all-cause mortality were found in the pravastatin group.

The Asymptomatic Carotid Artery Progression Study [19] was a randomized, double-blind, placebo-controlled multicentre trial in asymptomatic individuals with early carotid atherosclerosis and moderately elevated serum LDL-cholesterol; 910 individuals were followed for at least 33 months to determine the effects of lovastatin and warfarin on the progression of IMT. After 6 months, although IMT continued to progress in the placebo group, there was a progressive reduction in the lovastatin group. There was also a significant reduction in the incidence of cardiovascular events in the lovastatin group.

In the Kuopio Atherosclerosis Prevention Study [20], 447 men (mean age 57 years, range 44–65 years) with LDL-cholesterol greater than 4.25 mmol/l and total cholesterol below 8.0 mmol/l were randomized to receive pravastatin 40 mg/day or placebo for 3 years. There was a significant reduction in progression in the pravastatin group in the carotid, but not in the femoral arteries. There were eight fatal and nonfatal myocardial infarctions in the placebo group, and three in the pravastatin group. There is therefore some evidence that reduction in carotid IMT is accompanied by a reduction in cardiovascular events.

Coronary calcification detected by electron beam computed tomography

EBCT enables high-resolution images of the heart to be acquired in less than 100 ms. The rapid image acquisition time virtually eliminates motion artifact related to cardiac contraction. EBCT allows the detection, localization and quantification of calcification in the coronary artery tree. Methods have been developed to quantify accurately the burden of calcification detected by EBCT. The method of Agatston *et al* [21] has been the most widely used. Four major studies have assessed the predictive value of EBCT prospectively [22–25].

In a multicentre study [22], 491 symptomatic patients were followed for 30 ± 13 months for the definitive end-points of death and myocardial infarction; the ability of coronary calcification scores to predict events was compared with that of coronary angiography. Coronary calcification scores, but not the number of angiographically diseased vessels, significantly predicted the probability of a CHD-related event occurring during follow up.

Secci *et al* [23] followed 326 high-risk adults who had undergone EBCT for 32 ± 4 months. The combined definitive end-points of death, myocardial infarction and revascularization were at least three times as frequent in those with coronary calcium scores above the median.

Arad *et al* [24] followed 1173 asymptomatic individuals who had undergone EBCT for a mean of 19 months. They demonstrated that a calcium (Agatston) score of more than 100 yielded an odds ratio of more than 25, and a score of more than 160 yielded an odds ratio of more than 34 for the prediction of death, nonfatal myocardial infarction and revascularization.

However, a study reported by Detrano *et al* [25] of 1196 asymptomatic high coronary risk subjects who underwent risk-factor assessment and EBCT demonstrated that the coronary calcification scores failed to provide predictive power of cardiovascular events over and above risk factor assessment alone. On the other hand, we assessed 223 asymptomatic men aged 45–64 years with plasma cholesterol of 6.5 mmol/l or greater and demonstrated that more than one-quarter of those who were predicted to be at high-risk of cardiovascular events by conventional risk factors had no significant coronary calcification detected by EBCT [26].

One retrospective study [27] used the surrogate end-point of coronary calcification detected by EBCT to assess the effect of statins. The change in the calcium score over 12–15 months in 105 individuals who had received a statin was compared with the change in 44 subjects who had not received this treatment. A net decrease in the calcium score was observed only in the 65 treated individuals whose final LDL-cholesterol concentrations were less than 3.10 mmol/l.

Conclusion

With the exception of the 12-lead electrocardiogram, the surrogate end-points assess properties of vessel walls. Cardiovascular events involve the coagulation pathway as

well as the vessel wall, so that there are obvious limitations to the predictive powers of the surrogate end-points. The two most promising surrogate end-points are estimation of coronary calcification by EBCT and determination of IMT in carotid and femoral arteries by ultrasonography.

It is unlikely that the use of surrogate markers for cardiovascular disease could ever replace clinical end-point studies. However, there are some clear benefits to the use of surrogate markers in studies of cardiovascular disease. They provide information on the natural history and factors associated with progression. In trials that use clinical end-points, thousands of patients are usually needed to achieve sufficient statistical power. Using surrogate end-points every patient can provide an end-point and sufficient statistical power can be achieved with much smaller numbers of individuals. Smaller studies using surrogate markers can provide preliminary information on the effectiveness of new interventions and their mechanism of action.

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